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A Clinical Comparison of Three Commercial Estrogenic Preparations[1]

[Practical Use of Estrogens]

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SINCE POTENT estrogens have been available for clinical use there has occurred a pressing need for careful assay of these preparations on the human. All estrogens are active so that in selection for use certain attributes have been stressed, namely: *a*), mode of administration; *b*), cost; *c*), promptness of action; *d*), duration of action.

Among the estrogens available to the clinician there is no standard unitage to indicate their relative human potencies. Two commonly used preparations are estrone and estradiol benzoate. A separate and distinct international unit has been devised for each of these from which in turn their respective dosages are calculated. These international units consist of arbitrary weights of the crystalline materials without relation to their biological effects. No unit has been devised for diethylstilbestrol so that its unitage is sometimes based on its potency, which under certain conditions is two and one half times as great as that of estrone, i.e. if estrone has 10,000 I.U. per milligram, diethylstilbestrol is calculated to have 25,000 I.U. per milligram.

A series of estrogens when assayed in terms of rat units may have an entirely different dosage-potency ratio when assayed in terms of mouse units. Thus, Doisy (1) has shown that when alpha-estradiol and estrone are given in three portions during a 9-hour period, the alpha-estradiol is nine times as active as estrone if rats are used. Yet, it is only two times as active if mice are used.

This species difference has been recognized by other investigators (2–6) in their efforts to determine more nearly comparable human dosages. The interpretation of the results reported by various investigators has been difficult because each has his own human assay method. Thus, they have been unable to make more than general statements concerning the relative merits of the different estrogenic substances.

Doisy (1), who with Allen devised the Allen-Doisy rat unit for estrogens, states "that since bioassay has served its purpose in guiding chemists to the preparation of pure estrogens, it should now be discarded, the products for therapeutic use labeled in

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metric units and their evaulation effected by the response of patients."

Therefore, since neither international units nor rat units allow selection on the basis of clinical potency we have tried to clarify the dosage of estrogens by making an objective comparison of the effect of three estrogens in a selected group of women.

PROCEDURE

The general procedure used in assaying estrogens on test animals was followed as closely as possible (7). For accurate assays upon which reliable comparisons may be based, the following points are important: *a*), the use of large numbers of patients as closely alike as possible and without demonstrable ovarian activity; *b*), a fixed period of treatment for all of the hormones compared; and *c*), the taking of vaginal smears at regular intervals.

The importance of using large groups of individuals in any biological research is obvious because of the inevitable presence of a few highly sensitive and highly refractory individuals. Eight groups of ten to fifteen women each were treated with the specific dosage of the estrogen in question. The use of women in the postmenopausal period is the most practicable way of obtaining uniformity in the subjects. In the patients studied no ovarian activity was demonstrable from the vaginal smears taken prior to the institution of therapy. The women, all mental patients at the Ypsilanti State Hospital, ranged from 55 to 70 years of age, were on the same diet, and were not having sexual intercourse or intravaginal treatment.

Ten days was chosen as the period of treatment, because this is the approximate duration of the follicular or proliferative phase of the menstrual cycle.

The vaginal smear technique as described by Shorr (8) was used in this study. The classification of vaginal smear stages which we have devised incorporates some of the features of classifications developed by other authors (9, 10).

Over 1,800 slides were examined in this study, all by the first author. The reliability of the classification is attested to by the fact that when 200 of the slides were reclassified after a 6-month interval, 75 per cent were read identically. Most of the inconsistent interpretations were of the immature smear types. The smears which ranged from *stage* 4 to 9 were identically reclassified in 90 per cent of the cases. Since *stage* 4 to 6 is the important end point of the study, this degree of accuracy was felt to be satisfactory. Smears were taken at twice-weekly intervals before, during and after treatment, until the vaginal epithelium of all patients had returned to the atrophic state.

The pH of the vaginal secretion was determined with each smear. The potentiometer with calomel cells and a quinhydrone electrode was used during the early part of the study. Since such wide variations were found among different patients to the same dosage of the same estrogen, the simpler nitrazene and

TABLE 1. CLASSIFICATION OF VAGINAL SMEARS

Number	Stage	Leucocytes per High Power Field	Deep Cells per High Power Field	Vesicular Nuclei per High Power Field	Pyknotic Nuclei per High Power Field	Predominating Color
1	Atrophic	8–30	2–20	0–10	0	Blue
2	Atrophic-early	2–10	0–2	5–20	Occasional	Blue Green
3	Early	1–5	Occasional	15–25	Occasional	Green Blue
4	Early-moderate	0–3	Occasional	15–25	2–3	Green
5	Moderate	Occasional	0	Ratio 3:1		Green Red
6	Moderate-advanced	0	0	3:2 2:2 2:3		Green Red Red Green
7	Advanced	0	0	1:3		Red Green
8	Advanced-complete	0	0	1:4–5		Red Green
9	Complete	0	0	0-Occasional	All cells	Red

congo red indicator papers were used for the remainder of the study. Due to the wide variations measured by both techniques it was felt that vaginal pH was not an accurate criterion of estrogenic activity. This inaccuracy was likewise noted by Shorr (11).

The estrogens used in this study were alpha-estradiol benzoate, estrone and diethylstilbestrol.[3] The first two were given by intramuscular injection and the last by mouth.

The minimum amounts of the estrogens (given in the same daily dosage over a 10-day period), necessary to produce an estrous or midinterval vaginal smear (*stage 4–6*) in the middle 75 per cent of each group of patients on the day following cessation of treatment, were considered comparable.

Table 2. Results of clinical assay

Estrogen	Manufacturer's Estimate of Daily Dosage for 10 Days			Stage of Vaginal Smear Response on Day After Cessation of Treatment	Days After Cessation of Treatment Before Smear Returned to Atrophic Stage	Number of Patients
	Milligrams	International units	Rat units			
Diethylstilbestrol, orally	0.50	12,500		4–6	28	11
	1.00	25,000		5–6	29	12
	1.50	37,500		4–8	30	13
α-Estradiol benzoate, intramuscularly	0.33	20,000	2,000	4–5	22	12
	0.50	30,000	3,000	6–7	42	8
	0.83	50,000	5,000	6–8	44	13
Estrone, intramuscularly	1.00	10,000		4–6	29	12
	2.00	20,000		5–7	30	12

RESULTS

The observations of vaginal smear types shown in table 2 were all made on the day following the cessation of therapy, the day on which the peak effect was obtained with each dosage. In several patients the smear types were found to be the same on the 8th as on the 11th day of treatment, but in no case was the former higher. The range shown is that of the middle 75 per cent of the patients in each group.

It will be noted that the higher dosages of alpha-estradiol benzoate tended to show a more prolonged effect than the other groups. However, when the three preparations were given in comparable human dosages there was no appreciable difference in duration of effect.

Commercial claims lead the physician to believe that 1.0 mg. of estrone (intramuscularly), 0.17 mg. of alpha-estradiol benzoate (intramuscularly) and 0.4 mg. of diethylstilbestrol (orally) are equivalent.

This study has shown that 1.0 mg. of estrone (intramuscularly), 0.42 mg. of alpha-estradiol benzoate (intramuscularly) and 0.5 mg. of diethylstilbestrol (orally) are comparable dosages when assayed by our procedure on the human subject.

With dosages of the three estrogens which produced similar smear changes on the 11th day of treatment little difference is noted in the promptness or duration of response.

Table 3 illustrates the importance of basing the cost of estrogenic preparations on their human potency rather than on their rat or international unit potency.

Table 3. Comparative cost

Estrogen	Cost of Estrogen Based on Commercial Claim		Cost of Comparable Human Dosages	
Estrone	1.00 mg.	$1.25	1.00 mg.	$1.25
α-Estradiol benzoate	0.17 mg.	$0.42	0.42 mg.	$1.07
Diethylstilbestrol	0.40 mg.	$0.013	0.50 mg.	$0.016

DISCUSSION

Estrogens are used successfully in the human in a number of conditions associated with decreased ovarian activity. While the biochemistry of these substances after administration is poorly understood at present, they will continue to be used because they are effective.

The vaginal smear is a readily available index of estrogenic activity. Qualitatively, on the vaginal epithelium, the actions of the estrogens are indistinguishable. Some differences in estrogenic effects on other parts of the body may exist but they have not been proven to date.

Manufacturer's claims and costs have been based in large part on rodent vaginal epithelial changes.

[3] The estrogens used in this study were supplied by the following manufacturers: alpha-estradiol benzoate (as Progynon-B) by the Schering Corp., Bloomfield, N. J.; estrone (as Theelin) by Parke, Davis & Co., Detroit, Mich.; and diethylstilbestrol by the Upjohn Co., Kalamazoo, Mich.

Definite discrepancies are noted here, between units based on rodent and human response. Therefore, we feel that since patients are the recipients of estrogenic therapy, more regard should be given to human response.

SUMMARY

1. The assay of three commonly used estrogenic preparations: alpha-estradiol benzoate, estrone and diethylstilbestrol on a group of postmenopausal women has been studied by means of vaginal smear response.

2. Manufacturer's claims lead the physician to believe that 1.0 mg. of estrone, 0.17 mg. of alpha-estradiol benzoate and 0.4 mg. of diethylstilbestrol are equivalent.

3. On the human subject this study has shown that 1.0 mg. of estrone (intramuscularly), 0.42 mg. of alpha-estradiol benzoate (intramuscularly) and 0.5 mg. of diethylstilbestrol (orally) all produce the same results.

4. Diethylstilbestrol is far cheaper than the other two preparations by any method of assay.

5. Alpha-estradiol benzoate costs one-third as much as estrone according to manufacturing claims but it is nearly as costly when based on human response.

6. No appreciable difference was noted in promptness or duration of response to dosages of the three estrogens which produced similar smear changes on the 11th day of treatment.

7. The inadequacy of using a unit scale based on rodent response when dealing with human beings is emphasized.

The authors wish to express their appreciation of the assistance given by Miss Helen McRea in preparing the slides for this study.

REFERENCES

1. Doisy, E. A.: *J. Am. Med. Assoc.* 111: 501. 1941.
2. Kaufmann, C. L.: *Zentralbl. F. Gynäk.* 34: 2058. 1932.
3. Ibid.: *Proc. Roy. Soc. Med.*: 27: 858. Part II. 1934.
4. Werner, A. A., and others: Unpublished work exhibited at Am. Med. Assoc. Meeting, Scientific Exhibits, 1939.
5. Werner, A. A., and others: J. Am. Med. Assoc. 109: 1027. 1937.
6. Elden, C. A.: *Endocrinology* 20: 47. 1936.
7. Allen, E., C. H. Danforth and E. A. Doisy: Sex and Internal Secretions. Second Edition, Williams & Wilkins Co., Baltimore, 1939.
8. Shorr, E.: *Science* 91: 579. 1940.
9. Papanicolaou, G. N., and E. Shorr: *Am. J. Obst. & Gynec.* 31: 806. 1936.
10. Rubenstein, B. B.: *Endocrinology* 27: 843. 1940.
11. Shorr, E.: Personal communication.

Assay in the Human Female of Synthetic Estrogen, *118B*

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It is becoming increasingly well-known that the potency of estrogens, expressed in terms of biologic units as assayed in the laboratory, cannot be assumed to indicate the potency of estrogens in the human female. To avoid the confusion arising from the comparison of the activity of estrogens when determined by different laboratories and in different animals it has been suggested that therapeutic standards of estrogens be determined by assays in the human female (1). Several assays have been proposed using various criteria. One of us (2) has recently reported a technic for assay in women which uses the subjective relief of symptoms in menopausal patients as the indicator of estrogenic potency. In this method three dosage levels of estrogen are used, thus corresponding to the manner in which laboratory animals are assayed. The non-specific factors which interfere with the testing of menopausal patients are eliminated as much as possible by the proper selection of patients, using only those who have moderate to severe symptoms and eliminating those in whom there may be doubt as to the origin of the symptoms. In addition, non-specific factors associated with treating such patients are reduced to a minimum by the omission of suggestion, by changing of dosage without informing patients and by having one investigator evaluate the therapeutic response of all patients. The criterion of relief was based to a great extent on the amelioration of hot flashes, but changes in other conditions such as nervousness, depression and insomnia were also considered.

In this manner we have already assayed diethylstilbestrol and dihydrodiethylstilbestrol (hexestrol). The results indicate that diethylstilbestrol is approximately five times as potent as dihydrodiethylstilbestrol, the average minimal therapeutic dosages being for diethylstilbestrol 0.5 to 1.0 mg. by mouth daily and for dihydrodiethylstilbestrol 2.5 to 5.0 mg. by mouth daily.

We wish to report the assay in women of a synthetic estrogen, *118B*, a substance which has no chemical relationship to the stilbenes or the natural estrogens but which is claimed to be relatively active by oral administration.[1]

Patients complaining of moderate or severe menopausal symptoms were given at different times the daily dosage levels of 1.0, 2.5 and 5.0 mg. of *118B*. The initial dosage was administered for three weeks, at which time an evaluation of symptoms was made and which in table 1 is signified as 1+, indicating slight relief; 2+, satisfactory relief; 3+, complete relief. After the therapeutic response was evaluated the dosage level was changed and after three or more weeks the therapeutic response again was evaluated. This procedure was repeated the third time. The data in table 1 indicate the results.

Table 1. Relief of menopausal symptoms following different dosage levels of the synthetic estrogen *118B*

Daily Oral Dose					
1 milligram		2.5 milligrams		5 milligrams	
Number of Patients	Response	Number of Patients	Response	Number of Patients	Response
4	Negative	3	Negative	2	Negative
7	+	9	+	2	+
17	++	18	++	8	++
4	+++	8	+++	7	+++

From these results it can be seen that 1.0 to 2.5 mg. daily of the synthetic estrogen *118B* by mouth is a satisfactory therapeutic dose. This compares favorably with the average dose of diethylstilbestrol which is 0.5 mg. to 1.0 mg. daily. The relief of symptoms in patients after administration of *118B* could not be distinguished from that obtained with the stilbenes or with the natural estrogens. Only three patients experienced toxic reactions. One patient received 2.5

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[1] The synthetic estrogenic substance (118B) was supplied by Schieffelin and Company, New York N. Y.

mg. daily and two received 5.0 mg. daily. The untoward symptoms of all three were slight or moderate nausea. This lack of toxic symptoms following the use of *118B* offers a marked advantage over the use of diethylstilbestrol and hexestrol.

CONCLUSION

A daily oral dose of 1.0 to 2.5 mg. of the synthetic estrogen *118B* will produce satisfactory therapeutic response in the majority of menopausal patients. At the therapeutic level this estrogen is relatively free from toxicity.

We wish to express our gratitude to Miss B. Kretscheid, R.N., for her aid in this work.

REFERENCES

1. FREED, S. C.: Present status of commercial endocrine preparations. *J. Am. Med. Assoc.* 117: 1175. 1941.
2. FREED, S. C.: Estrogen Assay in the Human. Herbert M. Evans Anniversary Volume. In press.

Cyclical Endometrial Response to Prolonged Administration of Estradiol in the Castrate Woman

[Castration and Endometrium]

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THE OCCURRENCE OF periodic hemorrhages in the course of prolonged treatment with equal and constant doses of estrogens in castrated women and female monkeys is an important experimental fact in the knowledge of menstruation. Werner and Collier (1) injected castrate women daily with 100 to 300 I.U. of estrone in a watery solution, for a period of several months. Periodic uterine bleeding occurred during the treatment. Hisaw (2), Corner (3) and Zuckerman (4) obtained the same result in castrated female monkeys injected with moderate doses (approximately 100 I.U.) of estrone daily for a year. Bleeding recurred at intervals of 5 to 7 weeks. When Zuckerman repeated the experiment (5) using larger doses of estrone, he found that bleeding did not occur during the period of one year in which the castrate monkey received 1000 I.U. of estrone daily. Bishop (6) described 'threshold' bleeding which occurred periodically in a castrate woman receiving 5000 to 6000 I.U. of estrone. Reynolds, Kaminester and Schloss (7) administered estradiol dipropionate parenterally and estradiol orally to a castrate woman for a period of 5 months. Bleeding occurred three times in this patient at intervals of 18, 28 and 68 days. Davis (8) observed the recurrence of bleeding in amenorrheic women receiving 1 mg. of diethystilbestrol daily, even during the period of therapy.

Previous study (9, 10, 11) has shown that the vagina of the castrated rat responds rhythmically to estradiol. The present investigation was undertaken to determine if the endometrium of the intact uterus of the castrate woman will show a rhythmic response to estrogenic stimulation. The case is of special interest in that it is difficult to find a castrate woman whose uterus has been conserved, and who is willing to take daily injections of estrogen for five months.

CASE REPORT

The patient, *E. B.*, aged 45, had had a double oöphorosalpingectomy performed 14 years previously (for cystic ovaries) and had been amenorrheic since. The vaginal smear (fig. 1) revealed 80 per cent superficial spinous cells, 20 per cent deep spinous cells, and numerous leucocytes. A biopsy specimen of the vagina was composed of a thin superficial epithelium and a deeper layer of 2 to 3 row of cells. No biopsy of the endometrium could be obtained.

On May 24, 1940, daily injections of 200 international benzoic units of estradiol benzoate were begun. Fifty-three days later, on July 17, the dosage was increased to 400 I.U. daily, and maintained at that level until December 14 of the same year.

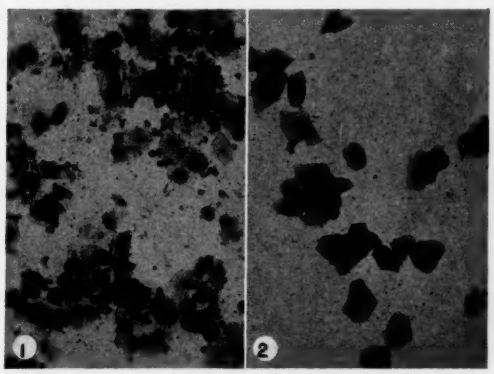

Fig. 1. VAGINAL SMEAR BEFORE TREATMENT.
Fig. 2. VAGINAL SMEAR AFTER 6800 I.B.U. OF ESTRADIOL BENZOATE

During the period of treatment uterine bleeding occurred 4 times and lasted 2 to 5 days each time. The first period of bleeding appeared 60 days after the treatment was started, and the remaining periods were separated by intervals of 60, 32, and 29 days, respectively. Two days after the last injection profuse bleeding occurred.

Repeated biopsies of the endometrium revealed a state of proliferation and the development of glandu-

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lar hyperplasia. Vaginal smears gave evidence of epithelial response to the estrogenic hormone (fig. 2). Figure 3 presents the data schematically.

DISCUSSION

The estrogen-withdrawal theory of menstruation (12) fails to explain the recurrence of bleeding from an endometrium under a sustained stimulation by injected estrogens. Allen, Hisaw and Gardner (13) suggested that bleeding from an endometrium under a continuous level of estrogen stimulus occurs when the amount of the proliferated endometrium becomes so great that the daily dose of 100 to 300 I.U. of estrogen is incapable of maintenance and thus the bleeding which occurs is the result of a relative estrogen deficiency. Such an explanation is plausible in cases in which watery solutions of estrone have been employed (1). However, if oily solutions of estradiol benzoate or dipropionate are used, absorption is slow, the effects are cumulative and the activity does not change over a period of time. Such preparations have been employed by Reynolds (7) and in our investigation, and the explanation of a relative deficiency is difficult to accept.

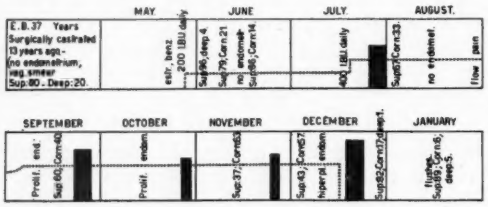

Fig. 3. CYCLICAL ENDOMETRIAL RESPONSE TO THE PROLONGED ADMINISTRATION OF ESTRADIOL IN THE CASTRATED WOMAN.

Previous experiments (9, 10, 11) have demonstrated that the vagina of the castrated rat periodically undergoes changes in its threshold of response to estradiol. The effect of acute adrenal insufficiency, injections of desoxycorticosterone and of progesterone on this threshold vaginal response was determined and the conclusion reached that "The vagina of castrated white rats possesses an intrinsic cyclical activity which is revealed by daily injections of adequate doses of estradiol; it is abolished by progesterone and desoxycorticosterone, and not influenced by hypophysectomy."

The cyclical vaginal response can be demonstrated by the implantation of pellets of estrone (unpublished data). Zuckerman likewise has observed the cyclic response of the vaginal epithelium of the castrate rat. He introduced the concept that the threshold of response of the endometrium to estrogens shows periodic fluctuations; bleeding occurs when the threshold of endometrial response surpasses the level of estrogen, thus producing a relative insufficiency.

In summary, these experimental facts show that two mechanisms may explain the appearance of uterine bleeding, *a*), a variation in the concentration of estrogens in the organism with reference to its diminution or suppression (the estrogen-withdrawal theory), and, *b*), the periodic fluctuation in the threshold of the response of the endometrium even though the concentration of the estrogens in the organism does not vary.

SUMMARY

The case of a castrated woman treated for 5 months with daily injections of 400 I.B.U. of estradiol benzoate is described. Uterine bleeding appeared four times at intervals of 60, 32 and 29 days during the course of treatment.

REFERENCES

1. WERNER, A., AND W. COLLIER: *J. Am. Med. Assoc.* 100: 633. 1933.
2. HISAW, F.: *Am. J. Obst. & Gynec.* 29: 638. 1935.
3. CORNER, G. W.: *Am. J. Physiol.* 113: 238. 1935.
4. ZUCKERMAN, S.: *Nature* 10: 139. 1937.
5. ZUCKERMAN, S.: *J. Physiol.* 92: 13. 1938.
6. BISHOP, P. M.: *Brit. M. J.* 1: 939. 1938.
7. REYNOLDS, S., S. KAMINESTER AND S. SCHLOSS: *Proc. Soc. Exper. Biol. & Med.* 45: 749. 1940.
8. DAVIS, R.: *Am. J. Obst. & Gynec.* 39: 938. 1935.
9. DEL CASTILLO, E. B., AND C. CALATRONI: *Rev. Soc. argent. de biol.* 2: 108. 1930.
10. DI PAOLA, G.: *Rev. Soc. argent. de biol.* 15: 61. 1939.
11. DEL CASTILLO, E. B., AND G. DI PAOLA: *Rev. Soc. argent. de biol.* 16: 563. 1940.
12. ALLEN, E.: Sex and Internal Secretions. Williams & Wilkins, Baltimore, 1939.
13. ALLEN, E., F. L. HISAW AND W. U. GARDNER: Sex and Internal Secretions. Williams & Wilkins, Baltimore, 1939.

Estrogenic Substances in Treatment of Pigmented Areas

[Estrogens and Pigmentation]

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THE LOCAL effect of estrin, first demonstrated independently by Zondek (1) and Mussio Fournier (2) and later confirmed by a number of investigators, has been used in the treatment of certain diseases of the skin and mucosae. The results obtained in facial hypertrichosis, juvenile acne, vulvar pruritus and kraurosis bespeak the ability of the skin to absorb the estrogenic substances as applied either in greasy excipients or in alcoholic solutions. We have been able to verify a new local effect of such substances which we believe has not yet been reported in the literature. In the observation reported here the topical application of an ointment containing estradiol caused a number of facial pigmented patches to disappear in a female patient in whom they had already become of a less intense hue following the injection of estrin.

CASE REPORT

The patient was an Uruguayan woman, married, aged 54 years.

Personal history. Childhood, normal. Menarche at 15. The menses have always been regular and painless. Marriage at 16. Nine children, the youngest of which is 9 years old at present. Pregnancies and parturitions, normal.

In 1937 signs of marked hypothyroidism were observed, with a basal metabolic rate of minus 29 per cent. The patient's hypothyroid disturbances improved with thyroid, which she had for only two months.

She came under our observation in October, 1939, her chief complaints being cardiac, circulatory, and climacteric vasomotor disturbances. The patient still menstruated and no hypothyroid signs were present.

We realized presently that the patient had some facial brown-colored pigmented areas scattered around the eyes, at the eyebrows and in the superciliary region predominantly on the left side, as well as about the zygomatic regions and the cheeks (fig. 1). Similar patches were found on the left arm and on the lower portions of both forearms, and also about the hands and knees.

The most confluent and widespread patches were those on the face. Their form and distribution were irregular and the skin was smooth and thin at their level, normal in appearance and without manifestations of vitiligo. The patient stated she had had the patches on the face and forearms for a number of years. Seven years ago a dermatologist instituted electrocoagulation therapy, and since then discolored striae have been present on the cheeks. The patches had increased in number and size in the past year.

Physical examination, October, 1939. Height, 154 cm., (5 ft.), Weight, 56 kg., (123 lb.). General health, good. The skin is thin and there is no dryness. The facies show a certain degree of puffiness. The presence of the pigmented patches and their distribution has been already indicated. The hair is dry, coarse and scanty on the scalp; some is gray. There is a thinning of the outer half of the eyebrows.

Fig. 1. FIFTY-FOUR-YEAR-OLD PATIENT, OCTOBER, 1939.

The eyes are brown and the sclera is blue. *Mouth.* There are numerous caries and paradentosis. The musoca is free from pigmentation. *Neck.* The neck is thin and the thyroid gland is not palpable. No supraclavicular fat pads are present.

Thorax. Lungs, normal sounds. Heart, normal. Pulse rate, regular and 72 per minute. Blood pressure, systolic 110, diastolic, 75 mm. Hg. Eczema is present on the anterior portion of the chest and submammary folds. *Abdomen.* Viscera, not palpable. The vesicular region is tender. *Extremities.* Negative findings upon examination with the exception of the pigmented patches already pointed out. *Neurological examination.* No noteworthy findings recorded. The patient is of a quiet disposition. She mentioned sensitivity to cold and slight perspiration. There is no constipation. The appetite has diminished.

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Sleep is normal, the memory poor. There is no asthenia. *Genitalia.* Normal in development. Irregular menses, with periods of amenorrhea of from 1 to 2 months.

Laboratory findings. Blood cholesterol, 219 mg. per cent. Blood urea, 20 mg. per cent. The Wasserman reaction was negative. Urine findings were normal. *Roentgenogram of the chest.* The heart and aorta are normal in appearance. *Electrocardiogram.* Normal tracings.

The histologic examination of a biopsy specimen of the pigmentation on the forearm showed the following characteristics. The pigment lies in the basal layer of the epidermis, within the cells, where it adopts a polar disposition, predominantly toward the superficial pole. At the borders of the patch the basal layer suddenly loses its pigment and the basal cells appear free from it. There are no pigment granules in the Malpighian layers. Important changes are found in the corium. A lymphoid infiltration is observed in the midst of a dissociated tissue, a dissociation which is probably due to edema. There is perivascular infiltration together with alterations of the walls of the vessels, which are predominantly thickened, but without sclerosis. From this histologic examination, as well as from the lack of pigment in the dermis, it is inferred that these are pigmentary patches and not pigmented nevi.

Fig. 2. (*left*). PATIENT AFTER TREATMENT WITH ESTRADIOL subcutaneously over a period of 2 months followed by treatment with estradiol in an ointment for a period of 20 days. Fig. 3. (*right*). PATIENT IN FEBRUARY 1941 ONE YEAR AFTER CESSATION OF THERAPY.

Treatment. Estrin was prescribed (estradiol subcutaneously) at a dosage of 5000 I.U. twice a week, up to January, 1940. The patient's menses became regular and her subjective disturbances were relieved. The patches about her face turned to a lighter color. An ointment of estradiol containing 250,000 I.U. in 50 gm. of excipient was then applied to her face for 20 days. A few patches were observed to disappear, while others showed a rather lighter hue (fig. 2).

Both the local treatment and the injections were continued. In September, 1940, the pigmentation had noticeably diminished on the face as well as in many other parts of the body, although it persisted chiefly about the forearms and hands.

The local treatment with estrin and the injections of the same substance were discontinued. The pigmentation continued to improve and in February, 1941, the patches on the face had completely disappeared (fig. 3). Although the patches on the forearms and hands still persisted, they were less marked than before. The patient has continued menstruating. At present (September, 1941) she presents small patches which have reappeared some time ago about the eyebrows. During this year she has received no hormonal treatment at all.

COMMENT

The appearance of pigmentary patches is not infrequently met with in the menopause, though they usually are not of such a dark color as in our case. It is also encountered in ovarian diseases and is a common sign during pregnancy. Marañón (7) has studied the influence of the pituitary gland on these dyschromias. Melanogenesis is inhibited through the sympathetic pathways, and, on the other hand, is stimulated by the hypophyseal melanophoric hormone. It is generally admitted that during menopause there is an increase in pituitary activity, as evidenced by the clinical signs and hormonal estimations. The ovarian deficiency would probably be the determining factor for this endocrinopathy. Among the consequences of this glandular imbalance is the disturbance of the pigmentary processes. The influence of estrin on melanogenesis concerns chiefly the normal distribution of the pigment. The effect of estrin on the pigmentation of the areola has been experimentally demonstrated by Lipschütz and other investigators (3, 4).

Zondek, (5) has been able to bring about an increase in the pigmentation of the areola by applying estrin locally.

Such results are positive only in those regions normally showing pigmentation, and, as Vilter (6) states, it has not been possible to induce pigmentation by means of estrin in other areas of the skin. On the contrary, and as we have verified in our patient, it is admissible that the estrin causes the disappearance of the abnormal pigmentation through a local effect on the melanocytes when it is applied on the skin or when it acts on the pituitary gland if used in injections, thus inhibiting the melanophoric hormone.

SUMMARY

The case is reported of a climacteric patient, to whom estrin was administered first locally and then by injection because of areas of pigmentation on the skin. Pigmentary patches on the face disappeared.

REFERENCES

1. ZONDEK, B.: *Lancet* 1: 1107. 1938.
2. MUSSIO-FOURNIER, M., AND A. ALBRIEUX: *Presse méd.* 47: 844. 1939.
3. LIPSCHÜTZ, A.: *Compt. rend. Soc. de Biol.* 108: 848. 1931.
4. LIPSCHÜTZ, A., AND M. MERINO: *Compt. rend. Soc. de biol.* 111: 421. 1932.
5. ZONDEK, B.: *Schweiz med. Wchnschr.* 65: 1168. 1935.
6. VILTER, F. W.: *Ann. de biol.* 6: 1935.
7. MARAÑÓN, G., AND C. RICHET: Estudios de fisiopatología hipofisaria, Buenos Aires, 1940.

Association of Uterine Fibromyomas with Other Clinical Conditions

[Uterine Fibromyomas]

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IN 1922 the simultaneous occurrence of tumors of the uterus, thyroid and breast was reported (1). In a series of 200 cases (100 uterine myomata and 100 goiters) fifty-three patients, or 26.5 per cent, had both goiter and uterine myomata. Five per cent had breast tumors.

The present report is based on 410 cases of Caucasian women with uterine fibromyomas. The ages ranged from 22 to 55 years, the average age being 42 years.

Three hundred and forty-eight of the patients (85%) were married. Of these, 75 (21%) had never been pregnant; 84 (24.5%) had had one or more spontaneous miscarriages.

One hundred and twenty-nine (37%) had migraine headaches. Two hundred and fifty-three (63%) had a goiter. Of this number 83 (33%) had a subsequent thyroidectomy.

Of the 410 patients with uterine fibromyomas, 268 (65%) had a hysterectomy. Seventy-seven (18%) had radium therapy for the uterine fibromyoma. Since 268 had a hysterectomy there remains a balance of sixty-five (15%) who were neither operated upon nor had radium therapy. These procedures may have been carried out elsewhere.

One hundred and sixteen (28%) had some form of arthritis, the majority of cases being classified as osteoarthritis or hypertrophic arthritis.

Sixty (22%) of the 268 operated cases had in addition a cholecystectomy for cholelithiasis. An additional 23 of the remaining 142 not operated upon had evidence of cholelithiasis by the Graham dye method of study—a percentage of 16. The total of all cases having cholelithiasis, diagnosed either at operation or by roentgen-ray study, was 83 (20%).

Three hundred and fifteen (75%) had one or more members of the immediate family who were 72 inches or more in height.

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Blood pressure readings were made on 362 patients. These were as follows.

Number of Cases	Percentage	Systolic Pressure *mm. Hg*	Age Range *Years*	Average Age *Years*
22	6.1	80–100	30–48	38.0
103	28.1	100–120	18–54	38.5
132	36.5	120–140	19–60	41.8
64	17.7	140–160	27–62	44.2
24	6.6	160–180	33–55	45.1
17	4.6	180–270	35–63	47.4

The systolic pressure ranged from a low of 80 to a high of 270 mm. Hg; the average age of this group of 362 patients was 40.8 years.

Twenty-two (5%) of the 268 operated cases had a subsequent operation for intestinal obstruction. Twenty (5%) of the 410 patients had hearing defects. Twenty-two (5%) had mastitis. Twenty-four (5%) had tumors of the breast divided as follows: cystadenoma 10; adeno-carcinoma 3; simple adenomas 11. The total number of patients with breast involvement was 46 (11%).

COMMENT

The average age of 42 years for this series of cases corresponds with that of the series of Costolow (2) who reported the average age of 986 patients with uterine fibromyomas as being 42.5 years.

The majority of the patients (85%) were married and 21 per cent were childless. In the menstrual history of these women the fact was noteworthy that most of them stated that the cycle was irregular from the time of menarche. Periods of amenorrhea followed by menorrhagia was a common complaint, showing that a predisposition was present from the beginning of the menarche.

The high incidence of migraine headaches seems to be greater than is usually encountered in association with other diseases. In a series of 100 patients

with migraine 70 per cent of 51 female and 80 per cent of 21 male patients had one or more members of the immediate family who were 72 inches or more in height (3). The combination of familial tallness, migraine headaches and uterine fibromyoma may have some significance as indicating a common etiological factor.

The association of goiter with uterine fibromyoma has been noted by many others. Freund (4) found that of 56 women with uterine fibromyoma 44 (approximately 80%) had a goiter. V.Graff (5) in a study of 112 women stated that 31 (27.7%) had a goiter. Ségond (4) Ullmann (6), Fraenkel (7) and many others have noted the high incidence of this combination.

It is of interest that none of the goiters in this series was classified as belonging to the exophthalmic type. In diagnosing a goiter as adenomatous, the impression gained by palpation that it is nodular determines the clinical diagnosis. This diagnosis is subject to error and to be accurate requires the verdict of the pathologist, as well as of the surgeon at the time of operation. Of the 253 women with goiter, 83 (33%) had the goiter removed and the specimens were all reported as being adenomatous. The clinical impression, therefore, seems to be fairly accurate and one is safe in saying that a large number of women with uterine fibromyoma have a goiter, regardless of whether it is adenomatous in character or not.

It will be noted that this series of patients with uterine fibromyoma consists entirely of Caucasian women. It is a well known fact that Negro women have a much higher incidence of uterine fibromyoma than Caucasian Women (8–12). On the basis of the present data, as well as that of others, the incidence of adenomatous goiter in the colored race should be much higher than in the Caucasian. Such is not the case, however, and in fact the reverse seems true.

An explanation of this is purely a speculative anthropological problem. Elsewhere (13) it has been pointed out that the mesoderm of the Negro showed certain singular characteristics when compared with that of the Caucasian. This tissue in the Negro is particularly susceptible to disease whereas the ectoderm is relatively immune. The mesoderm gives rise to the tissues comprising the uterine fibromyoma. The close physiological relationship existing between the pituitary gland, the uterus and the thyroid is well-recognized.

Freeman (14) has shown that the Negro race has a heavier pituitary gland than the Caucasian if the pituitary weights of the same sexes are compared. If one assumes that the heavier gland in the Negro means more activity and therefore that it secretes an increased amount of thyrotropic hormone, then the lower incidence of goiter or thyroid enlargement in the Negro is puzzling. Of course glandular enlargement does not necessarily mean increased function, as witness the hypofunction of the goiter in cretins, and the chromophobe adenoma of the pituitary. However, the cellular morphology of the Negro's pituitary, as well as the clinical evidence, points to as great activity, if not greater, than that found in the Caucasian.

The influence of the thyroid gland on both the development and function of the ectodermal nervous system has been amply verified. The relative immunity to disease of the ectoderm in the Negro has been pointed out (13, 15). The development of the nervous system in the Negro is not as great as in the Caucasian considered in the higher sense of psychic and intellectual development. The Negro does not suffer from diseases of the nervous system in any comparable statistical frequency as compared to the Caucasian.

Is the relative immunity of the ectoderm in the Negro accounted for by the fact that thyroid disease is less frequent, or, put in another way, does the relative inactivity of the thyroid in the Negro account for the lack of nervous system involvement? In other articles (16, 17, 18) data have been submitted showing the embryohormonic relations of the thyroid gland to ectodermal tissues. Having a bearing on the present discussion of the lessened incidence of goiter in the negro, as well as the relative immunity of their nervous system is the following:

Davenport (19), speaking of the geographical distribution of multiple sclerosis as found in the recruits of World War I said: "The resemblance between the distribution of multiple sclerosis and chorea is considerable except that chorea is abundant also in Texas, Mississippi, Missouri and the states of the North Atlantic coast and of the eastern slopes of the drainage basin of the Ohio River. That is, high rates for chorea are more widespread than for multiple sclerosis. The resemblance of the distribution of multiple sclerosis to that of simple goiter is somewhat striking. In both diseases, comparatively few cases are found south of the Ohio River. The maximum rate is in Michigan, Wisconsin and the extreme Northwest. The Negro race is not immune to the disease; although as indicated it, including mulattoes, is probably less subject to the disease than the white race." In Davenport's table the percentage distribution of multiple sclerosis among injuries and diseases of the nervous system, as determined in certain classified races, showed that the African percentage was 3.5 in 511 cases of multiple sclerosis; only the Dutch, who had a percentage of 1.0, had a lesser incidence than the African. The Scandinavian race had the highest percentage, being 12.5; the French 10.7; Slav 9.0; German 8.3; Scotch 8.2.

Brain (20) states that multiple sclerosis is most prevalent in Northern Europe and Switzerland. The

latter country, as we know, is noted for its high incidence of goiter. Brain says that in England and Wales there are approximately 200 cases of multiple sclerosis per million living persons or 1 in 5000. In Switzerland the incidence is nearly double. This adds support to Davenport's observations that where goiter is endemic there multiple sclerosis seems to be more prevalent. The maximum rate for multiple sclerosis in drafted men was found in the states of Michigan and Minnesota, each having 18 per 100,000.

In my series of 410 uterine fibromyomas with 253 (63%) having goiters, there were 6 cases of multiple sclerosis. This would give a percentage of 1.46. Five of the 6 cases with multiple sclerosis had a goiter. In one family of a tall Swedish type, was one member who had a hysterectomy for a fibromyoma and a thyroidectomy for a toxic goiter. She died with multiple sclerosis which preceded the symptoms of fibromyoma by several years. Her brother also died with multiple sclerosis, the diagnosis in both instances having been confirmed in other institutions. One sister had a thyroidectomy for toxic goiter and another sister had a hysterectomy for fibromyoma and the latter also had a nodular goiter.

Another patient developed symptoms of multiple sclerosis at the age of 22 and had a hysterectomy at 34 for uterine fibromyoma. She died one year later from the complications of multiple sclerosis.

Davenport (19) in discussing the geographic distribution and race of those having multiple sclerosis said "Various hypotheses are suggested for these facts. One is that there is some race inhabiting the Great Lakes region and the State of Washington that is especially subject to multiple sclerosis as well as goiter, chorea and cardio-vascular defects. One thinks of the big Swedes that live in this country. Probably the cardiovascular defects are associated with the tall stature of men from this locality."

It is of interest that as shown in the present series, tallness was present in a majority of patients' families.

That the nervous system of the Negro differs in many respects from that of the Caucasian is supported by much evidence. The Negro seems relatively immune to chorea (21). It is a well-known fact that the Negro's nervous system suffers much less from syphilis than does that of the Caucasian. Fairbairn (22), for instance, says that in a discussion on neurosyphilis in the tropics all of the speakers stated that this condition is rare and very few cases were reported, although all of them had had extensive experience with work in the tropics. Zieman (23a) said that he had only seen two cases among West Indians. Kirschner (23b) saw two cases in 3800 native patients. Kelly (24) said that tabes dorsalis and general paralysis of the insane were infrequent and the few cases of the latter which were seen generally occurred among those who did not perform hard manual labor. Cook (25) said that in the Protectorate very few cases of locomotor ataxia or dementia paralytica were to be seen and he could not recall seeing one case of general paralysis of the insane among the population. Nelson (26), Noronha (27), Pearce (28) and many others agreed that neurosyphilis is rare in the natives of the tropics. Lehmann (29) gave the percentage of tabes dorsalis in the Caucasian as 80 per cent and only 20 per cent in the Negro.

Paskind (30) from the results of his studies concluded that the Negro is less susceptible than the Caucasian to the central action of atropine.

Vint (31) found the brain of the Kenya native to weigh 10.6 per cent or 152 gm. less than the average weight given for the brain of the European. Miller (32) said that the nervous system of the Negro exhibits a lessened sensibility to pain and shock and that the pure black type is the safest surgical risk to be found in our hospitals, although the mulatto is a poorer surgical risk than either of the pure races.

Of interest is the rarity of ectodermal epithelial involvement in the Negro. The fragmentary evidence available seems to justify the conclusion that malignant tumors in the slave population were extremely rare corresponding in this respect to present day conditions in practically all parts of Africa.

Hoffman (33), in studying the statistics of the Metropolitan Life Insurance Company for the years 1911 to 1922, found that the rate for cancer of the skin was 2.1 per cent for Caucasian males and 0.7 per cent for colored males; the rate for the female Caucasian was 1.6 per cent and the Negro was 0.8 per cent. Cancer of the skin constituted only 1.4 per cent of the Negro deaths from cancer in the United States during 1923 to 1927. In the total American population in 1927 this proportion was 2.8 per cent. Thus there is a marked difference in favor of the Negro in cancer of the skin which is deserving of consideration. In Detroit for the year 1930 the Caucasian rate for cancer was 75.6 and the Negro 38.3. (34).

The relatively high incidence of arthritis in women who have uterine fibromyomas is no doubt of some importance. Since the etiology of the uterine fibromyomas and arthritis are both unknown, speculation is useless. The same may be said for hypertension. It will be noted that 105 (29%) of the 362 patients who had the blood pressure recorded had systolic readings ranging from 140 to 270 mm. Hg, and the average age of this group was 45 years. Approximately one-third of the series, therefore, have either a mild or severe hypertension. Of course these patients are in the age level at which hypertension is apt to occur, but this does not detract from the fact that there is a sizable number who have this condition.

SUMMARY

A series of 410 uterine fibromyomas associated with other clinical conditions is reported in Caucasian women. The average age in the series was 42 years.

Two hundred and sixty-eight (65%) had a hysterectomy. Sixty-seven (18%) had radium therapy. Two hundred and fifty-three (63%) had goiter. One hundred and twenty-nine (37%) were subject to migraine headaches. One hundred and sixteen (28%) had some form of arthritis, the majority of cases being classified as osteoarthritis or hypertrophic arthritis.

Sixty (22%) of the 268 hysterectomized cases had cholelithiasis.

Three hundred and fifteen (75%) had one or more members of the immediate family who were 72 inches or more in height.

One hundred and five (29%) of 362 patients whose blood pressure was recorded had systolic readings from 140 to 270 mm. Hg. The average age of this group was 45 years.

Attention was called to the fact that uterine fibromyomas are more common in Negro women. On the basis of a high incidence of adenomatous goiter in Caucasian women with fibromyomas, as shown in this series, Negro women should show a much greater incidence of goiter. Such is not the case and a racial singularity was invoked to explain the difference.

REFERENCES

1. Ballin, M., and R. C. Moehling: Simultaneous occurrence of tumors in the thyroid, uterus and breast. *J. Am. Med Assoc.* 79: 1243 1922.
2. Costolow, W. E.: Uterine fibromyomas. *J. Am. Med. Assoc.* 116: 464. 1941.
3. Moehlig, R. C.: Migraine: Study based on one hundred cases. *Endocrinology* 15: 11. 1931.
4. Kraus, E. J.: In Veit, J.: Handbuch der Gynäkologie. Herausgegeben von Walter Stoeckel. Band IX. Die Bedeutung der inneren Sekretion für die Frauenheilkunde, bearbeitet von Walter Berblinger et al. 3rd ed. J. F. Bergmann, München, 1936.
5. Graff, E. v: Schilddrüse und Genitale. *Arch. f. Gynak.* 102: 109. 1914.
6. Ullmann, E.: Uber Beiziehungen Zwischen Uterusmyon und dem Kropf. *Wien. klin. Wchnschr.* 23: 585. 1910.
7. Fraenkel, M.: Beiziehungen Zwischen Schilddrüse und Genitale bei beiden Geschlectern. *Deutsche med. Wchnschr.* 1: 108. 1924.
8. Matas, R.: The surgical pecularities of the American negro. *Tr. Am. S. A.* 14: 483. 1896.
9. Witherspoon, J. T., and V. W. Butler: The etiology of uterine fibroids with special reference to frequency of their occurrence in negro, hypothesis. *Surg., Gynec. & Obst.* 58: 57. 1934.
10. Miller, C. J.: A comparative study of certain gynecologic and obstetric conditions as exhibited in the colored and white races. *Tr. Am. Gynec. Soc.* 53: 91. 1928.
11. Ballach, E. A.: Relative frequency of fibroid process in the dark skinned races. *News* 46: 29. 1893.
12. Alsobrook, H. B.: One thousand cases of uterine fibroid in the negro race. *New Orleans M. & S. J.* 84: 317. 1931.
13. Moehlig, R. C.: Mesoderm of the negro. *Am. J. Phys. Anthropol.* 22: 297. 1937.
14. Freeman, W.: The weight of the endocrine glands: biometrical studies in psychiatry. *Human Biol.* 6: 489. 1934.
15. Holmes, S. J.: Resistant ectoderm of negro. *Am. J. Phys. Anthropol.* 12: 139. 1928.
16. Moehlig, R. C.: A study of ductless glands. *Detroit Medical Journal* 14: 268. 1914.
17. Moehlig, R. C.: Embryohormonic relations of thyroid gland to ectodermal tissues. *Ann. Int. Med.* 1: 400. 1927.
18. Moehlig, R. C.: *J. Michigan M. Soc.* 31: 525. 1932. cal studies in psychiatry. *Human Biol.* 6: 489 1934
19. Davenport, C. B.: Multiple sclerosis from the standpoint of geographic distribution and race. Association for Research in Nervous and Mental Diseases, Multiple Sclerois. Vol. II Paul B. Hoeber, Inc., New York, 1921.
20. Brain, R.: Diseases of the Nervous System. Oxford Medical Press Publication, 2nd ed., London, 1940.
21. Huddleson, J. H.: Cecil's Text Book of Medicine, 4th ed. W. B. Saunders Company, Philadelphia, 1937. P. 1472.
22. Fairbairn, H.: Tabes Dorsalis in an East African native. *Brit. Med. J.* 2: 382. 1933.
23a. Zieman, H.: see Wolff, *Arch. f. Schiffs-u. Tropen-Hygiene* 12: 645. 1908.
23b. Kirschner, L.: Quoted in *Tropical Dis. Bull.* 25: 12. 1928.
24. Kelly, R. W.: Imperial Social Hygiene Congress. *Brit. Med. J.* 2: 157. 1931.
25. Cook, A. R.: Imperial Social Hygiene Congress. *Brit. Med. J.* 2: 157. 1931.
26. Nelson, H.: Imperial Social Hygiene Congress. *Brit. Med. J.* 2: 157. 1931.
27. Noronha, M.: Imperial Social Hygiene Congress. *Brit. Med. J.* 2: 157. 1933.
28. Pearce, L. : Imperial Social Hygiene Congress. *Brit. Med. J.* 2: 157. 1931.
29. Lehmann, I. I.: Diabetes mellitus, syphillis and the negro. *Am. J. M. Sc.* 162: 226. 1921.
30. Paskind, H. A.: Some differences in response to atropine in white and colored races. *J. Lab. & Clin. Med.* 7: 104. 1921.
31. Vint, F. W.: The brain of the Kenya native. *J. Anat.* 68: 216. 1933.
32. Miller, C. J.: A comparative study of certain gynecologic and obstetric conditions as exhibited in the colored and white races. *Tr. Am. Gynec. Soc.* 53: 91. 1928.
33. Hoffmann, F. L.: Cancer in the North American negro. *Am. J. M. Surg.* 14: 229. 1931.
34. Bulletin, Detroit Board of Health, 1930.

Effect of an Excess of Ingested Carbohydrate upon the Glycogen Content of Vaginal Epithelium

[Vaginal Cell Glycogen]

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That glycogen is present in the epithelial cells of the vagina has been recognized for years, but factors responsible for quantitative changes in glycogen have not been investigated in detail. In the past such studies required a complicated staining technic. Since the introduction of the iodine vapor method by Mack (1) this obstacle has been overcome and future studies should be easier and may reveal valuable information concerning the physiology of the female generative tract.

The presence of glycogen in the vaginal cells of newborn infants and sexually mature women, with a decrease or complete absence during childhood and the postmenopausal period suggests that the estrogenic hormone plays a part in its deposition. This assumption is corroborated by the appearance of glycogen coincidental with the increase in cornification in the vagina of children undergoing estrogenic treatment for gonorrheal vulvovaginitis (2) and during substitutional therapy in menopausal women. The studies of McLaren (3) on postmenopausal women, however, show that the age limits within which glycogen has been assumed to be absent are too sharply drawn. He was able to demonstrate small amounts in all sections of the vaginal wall examined regardless of the time which had passed since cessation of menstrual periods.

Because our knowledge regarding factors responsible for glycogen mobilization in the vaginal mucosa is so meager this study was undertaken to provide information concerning the effects of an abnormally high carbohydrate diet upon the glycogen content of the vagina as shown by vaginal smears stained specifically for that substance.

METHOD OF STUDY

A group of 14 postmenopausal women was selected from the patients of the Ypsilanti State Hospital. The youngest subject was 64 years of age and the oldest 86. The selection was made from a larger potential group and these particular individuals were chosen because all demonstrated definite atrophic changes in the genitalia and none had any demonstrable physical or gynecological abnormality which might have influenced the results. All of the patients were ambulatory and on the general hospital diet.

Vaginal smears were taken twice weekly and stained for glycogen by the iodine vapor method. The glycogen content of the cells as demonstrated in this manner was compared at intervals with Best carmine stains on identical spreads. Shorr stains for cell type were made prior to and during treatment.

The glycogen smears were graded from + to ++++, the gradation being primarily on the basis of the number of glycogen-containing cells. The smears were read in the following manner:

+, only an occasional glycogen-containing cell.
++, less than one-third of the cells contained glycogen.
+++, from one-third to two-thirds of the cells contained glycogen.
++++, more than two-thirds of the cells contained glycogen.

The Shorr stains were graded according to the degree of cornification of the cells. Those definitely unstimulated were read as atrophic. The various degrees of cornification were recorded as early, moderate, advanced or complete.

After an initial period of three weeks of observation without treatment the patients were divided arbitrarily into three groups. During the remainder of the study the 5 patients in *Group I* were given 200 gm. of carbohydrate daily in excess of the general diet. After three weeks on the added glucose each was given 1 mg. of diethylstilbestrol daily for 12 days. Those in *Group II* (5 patients) were given no added carbohydrate but took diethylstilbestrol in the same

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manner and at the same time as those in *Group I*. The 4 patients in *Group III* were given 200 gm. of carbohydrate daily during the period of investigation but no estrogenic substance. The glucose was given in the form of clear hard candy and all of the subjects were kept under careful observation to insure their consuming the total amount of added glucose as well as the normal daily diet.

RESULTS

Glycogen content of the vaginal cells before treatment. Glycogen was found in the smears of every patient despite the fact that all showed definite atrophic changes in the genitalia and all were at least 12 years postmenopausal. While in some instances the amount of glycogen was small the smears from several untreated patients were read consistently as +++ (table 1). During the initial 3-week period of study without treatment little change was noted in the glycogen content. A comparison of the glycogen content and cell type (table 1) shows that in almost every instance in which the smears were graded as atrophic there were only small amounts of glycogen while in those in which there was more cornification the glycogen was deposited in a greater concentration. It is of interest that *patient 16* who was 86 years of age consistently showed a moderately advanced stage of cornification of the vaginal mucosa and glycogen in about half of the smeared cells.

Table 1. Pretreatment vaginal smear examinations

Patient	Age, Years	Average Glycogen for 3 Weeks Before Treatment	Cell Type
1	66	++	Atrophic
7	79	+++	Early
10	68	+++	Early
13	64	++	Atrophic
16	86	+++	Moderate
2	80	++	Atrophic
3	73	++	Early
6	77	++	Early
8	84	+++	Atrophic
12	75	+++	Early
4	67	++	Early
5	70	+	Atrophic
11	73	+++	Atrophic
15	71	+	Atrophic

Glycogen response to the administration of carbohydrate. Nine patients (*Group I* and *III*) were given extra carbohydrate. In table 2 is tabulated the glycogen content of the vaginal cells during the 3-week period of carbohydrate administration as compared with the pretreatment smears. No increase in glycogen was noted except in *patient 15* in whom there was a change from + to ++ during the first week of glucose administration. The actual increase in the amount of the substance as observed in the smears, however, was very slight. No change in the cell type could be detected in the stained smears.

Glycogen response to the administration of diethylstilbestrol. In table 3 is shown a comparison of the response of the vaginal cells in *Groups I* and *II* to stimulation with diethylstilbestrol. In both groups there was a definite increase in glycogen content apparent within one week. The increase was noted as a greater concentration in the individual cells and an increase in the number of glycogen-containing cells. No differences in rapidity of response or in total quantity of glycogen deposited could be detected between the two groups although the subjects in *Group I* continued to take the added glucose.

The response as evaluated by increase in cornification of the cells likewise was not altered by the previous administration of carbohydrate. In both groups it was noted that an increase in the amount of glycogen could be observed before there was much alteration in cell type and also that a change to an advanced stage of cornification did not necessarily accompany a heavy glycogen infiltration (table 3, *patients 1, 13, 2*).

Three patients (*1, 10, 16*) had withdrawal bleeding following the administration of diethylstilbestrol. The flow was scant in amount, began two days after the drug was stopped and lasted two days.

Table 2. Glycogen content during carbohydrate administration

Patient	Average Pretreatment Glycogen Content	Glycogen Content During 3 Weeks of Treatment with 200 Grams of Excess Carbohydrate Daily					
1	++	++	++	++	++	++	++
7	+++	+++	++	++	++ +++	++	+++
10	+++	++	+++	+++	++ +++	++	+++
13	++	++	+++	++	++	+++	++
16	+++	+++	++	++	+++	+++	+++
4	++	++	++	++		++	++
5	+	++	+ ++	+	+	+	++
11	+++	+++	++	++	++	++	++
15	+	+	++	++	++	++	++

TABLE 3. GLYCOGEN CONTENT AND CELL TYPE DURING DIETHYLSTILBESTROL THERAPY

Patient	No Diethylstilbestrol		Diethylstilbestrol, 1 milligram Daily					
			4 Days Total, 4 milligrams		8 Days Total, 8 milligrams		12 Days Total 12 milligrams	
Group I	Glycogen	Cell type	Glycogen	Cell type	Glycogen	Cell type	Glycogen	Cell type
1	++	Atrophic	++	Atrophic	++	Atrophic	+++	Early
7	+++	Atrophic	++	Early	++++	Moderate	++++	Advanced
10	+++	Early	+++	Early	+++	Moderate	++++	Advanced
13	++–+++	Early	+++	Early	+++	Early	++++	Early
16	+++	Moderate	+++	Moderate	++++	Advanced	++++	Advanced
Group II								
2	++	Early	++	Early	++	Early	++++	Early
3	++	Early	+	Moderate	++	Advanced	+++	Advanced
6	++	Early	++	Moderate	++	Moderate	++++	Advanced
8	+++–	Atrophic	+++	Early	++++	Advanced	++++	Advanced
12	+++	Early	++	Early	++++	Moderate	++++	Moderate

SUMMARY

The ingestion of glucose by the normal human being results in a temporary rise in blood sugar which is followed by an increase in liver and muscle glycogen and possible glycosuria (4). This occurs regardless of the age of the individual and is the result of the protective body mechanism by which the blood sugar level is stabilized.

Variations in glycogen content of epithelial cells of the vagina appear to reflect the level of the estrogenic hormone in the body rather than the amount of carbohydrate available to the cells. If this supposition is correct the vaginal cells during childhood and old age, when the estrin production is at a minimum, should be devoid of glycogen. This study of the glycogen content as seen in vaginal smears from a group of women well past the menopause shows that small amounts of glycogen are present in all cases regardless of the age and degree of atrophic change in the tissues. This may be interpreted as indicating the presence of small amounts of estrin or else that estrin is not entirely responsible for the control of glycogen deposition in the vaginal epityelium.

An increase in the carbohydrate intake to a point well above average produced no noticeable change in the concentration of glycogen. A comparison of response to the administration of diethylstilbestrol in patients being given extra carbohydrate and in those on a normal diet revealed no change either in the rapidity with which the glycogen was laid down in the cells or in the total amount deposited during the test period.

The accuracy of the iodine vapor method for staining glycogen was checked by a comparison with identical slides stained by the Best carmine procedure. The amount of the material stained by the two methods was quantitatively comparable.

CONCLUSIONS

1. The results of a study of glycogen mobilization in the vaginal mucosa of postmenopausal women are presented here.

2. Glycogen was demonstrated in the vaginal smear of every patient regardless of her age.

3. The administration of excessive amounts of carbohydrate resulted in no change in the glycogen content of the vaginal cells.

4. Diethylstilbestrol, 1 mg. daily for 12 days, produced a definite increase in the amount of glycogen in all cases. No difference in response to the estrogenic substance was noted in patients on an abnormally high carbohydrate diet as compared with those whose sugar intake was normal.

5. The iodine vapor method of staining for glycogen is simple, inexpensive, and accurate.

REFERENCES

1. MACK, H. C.: *Harper Hosp. Bull.* 1: 54. 1942.
2. LEWIS, R. M.: *Am. J. Obst. & Gynec.* 26: 593. 1933.
3. MCLAREN, H. C.: *J. Obst. & Gynaec. Brit. Emp.* 48: 1. 1941.
4. BEST, C. H., AND N. B. TAYLOR: The Physiological Basis of Medical Practice. 2nd Edition. Williams & Wilkins, Baltimore, 1939.

Dermovascular Changes during the Menstrual Cycle: Failure to Find a Cyclic Variation in Contractile or Dilating Capacity of Capillaries of the Skin[1]

[Cyclic Vascular Changes]

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An effort was made to learn if a cyclic variation in the condition of the smallest blood vessels of the skin occurs from one menstrual period to the next. A number of correlations between somatic, functional states and menstruation have been claimed, a few demonstrated and others denied (1, 2, 3). By utilizing a new method for evaluating the threshold of contractile excitability of the smallest blood vessels of human skin in response to graded mechanical stimulation (4, 5) it was possible to learn if 'premenstrual tension' or premenstrual increase in body weight was correlated with a change in the functional capabilities of the smallest cutaneous blood vessels. In addition, data were obtained on the vasodilating capacity of these blood vessels by a method likewise recently developed. This second method grades the response of reactive hyperemia to a controlled pressure device for producing local circulatory stasis (5, 6). Briefly, the data from both series of tests failed to show any consistent variation in dermovascular responsiveness (contractility or vasodilating capacity) during the menstrual cycle.

Six women medical students and one research assistant, all in good health, and between 22 and 28 years of age were studied during a total of twenty-four menstrual cycles. The length of the cycles, and the number during which any individual was examined, are shown in figure 1. Strength-duration curves of capillary contractility were obtained 66 times in all. Data on reactive hyperemia were obtained more than one hundred and fifty times. The results may be summarized as follows.

Tests for vasodilating capacity (reactive hyperemia). The data from these women were obtained on the skin of the forearm from November, 1940 to June, 1941. At the same time, data were obtained on a group of 100 men of about equal ages. The two sets of data were wholly super-imposable, and showed a characteristic seasonal variation which has been reported in detail elsewhere (6). There was never any evidence that the threshold for reactive hyperemia varied with the menstrual cycle, even when observations were made a day, or a few hours before the onset of menstruation, nor was there any characteristic change during the period of blood flow, or near the middle of any of the cycles studied. Observations were made, for the most part, at weekly intervals, but at times which were thought might have been crucial in the menstrual cycle, observations were frequently made twice or three times weekly.

Tests for capillary contractility. Fewer data have been obtained with respect to these data than with the former. Sixty-six curves were obtained on the inner aspect of the forearm; in at least six menstrual cycles, curves of dermovascular excitability were obtained four to seven times. With respect to the rest, the days of the cycle on which the data were obtained was carefully kept; a written record of the length of each cycle was also kept.

In order to bring the data together, the days of a cycle were expressed as a percentage of the whole cycle. By the device shown in figure 1, the separate coefficients of excitability [reciprocal of the products of the rheobase[2] and the chronaxie, in a strength-duration curve (7)], are correlated with the relative times in the several cycles when the curves were obtained. Clearly, there is no clean-cut correlation between the contractile excitability of the blood vessels and the menstrual cycle. That it would have been

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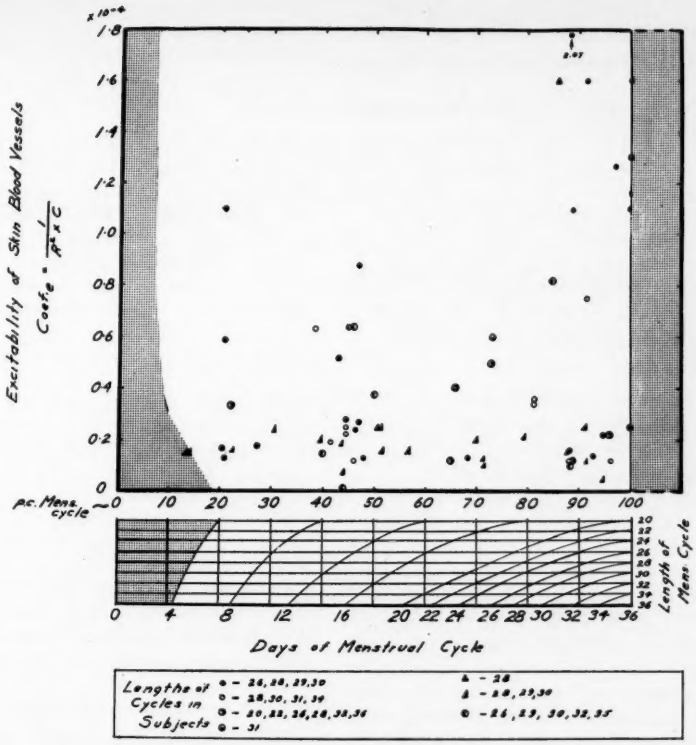
Excitability of Skin Blood Vessels
Coefficient = 1/A²×C
pc. Mens. cycle
Days of Menstrual Cycle
Length of Mens Cycle
Lengths of Cycles in Subjects

Fig. 1. Data showing lack of correlation between coefficient of excitation for capillary constriction in the skin in response to graded mechanical stimulation and the time in the menstrual cycle. (Stippled areas, period of menstruation represented as of 4 days' duration.)

Use of the nomogram: a) Find in the lower graph the figure for the day of the menstrual cycle on which an observation is made. *b)* Find at the right edge the number of days' length of that cycle. *c)* At the point of intersection of these two lines read at the top, *from the corresponding vertical ordinate*, the percentage value of the corresponding cycle. Examples: *A)* An observation made on day 16 (read at bottom) of a cycle 32 days in length (read at right) is at the 50% point (read at top) of the cycle. *B)* Day 16 of a 24-day cycle is 66% of the cycle. Similarly for any other day, or fraction of a day, if one chooses to read that closely.

detected if it existed is shown by the fact that other physiological and clinical conditions do affect the vascular excitability in characteristic ways (4, 5, 7).

CONCLUSION

Somatic physiological changes which occur during a menstrual cycle do not involve, or depend upon, cyclic alterations in dermovascular irritability, as measured by the ease with which capillary constriction may be elicited, or capillary dilation affected.

REFERENCES

1. Fluhmann, C. F.: Menstrual Disorders. W. B. Saunders Co., Co., Philadelphia, 1939.
2. Reynolds, S. R. M.: Physiology of the Uterus. Paul B. Hoeber, Inc., New York, 1939.
3. Evans, J. N.: *Tr. Am. Ophth. Soc.* 1940.
4. Di Palma, J. R., and F. I. Foster: In press.
5. Reynolds, S. R. M., J. B. Hamilton, J. R. di Palma, G. R. Hubert and F. I. Foster: *J. Clinical Endocrinology* 2: 228, 1942.
6. DiPalma, J. R., S. R. M. Reynolds and F. I. Foster: *Am. Heart J.* 23: 377. 1942.
7. Di Palma, J. R., S. R. M. Reynolds and F. I. Foster: *J. Clin. Investigation* 20: 333. 1941.

Dermovascular Actions of Certain Steroid Hormones in Castrate, Eunuchoid and Normal Men[1]

[Dermo-vascular Change]

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AMONG THE EFFECTS on somatic tissues of estrogenic and androgenic hormones, those involving the cutaneous blood vessels are particularly noteworthy. The evidence for this statement is both experimental and clinical. Clinically, both types of hormones have served to provide relief from flushes resulting from gonadal insufficiency. In this regard the actions are in part indirect, involving the central nervous system, and in part directly upon the blood vessels themselves (1, 2, 3).

From the experimental standpoint, androgenic substances have been shown to alter both the amount of blood in the cutaneous vessels, and the ratio of oxygenated to reduced hemoglobin (4). In general, the quantity of oxyhemoglobin increases relative to the amount of reduced hemoglobin, following injection of testosterone propionate into castrate and eunuchoid men. As for estrogens, these have been found to dilate the smallest blood vessels of the rabbit's ear (5) and to increase the amount of acetylcholine, a potent vasodilator, in certain tissues such as the uterus of the rabbit (1, 6), and the nasal mucosa of rabbits and cats (7).

The above mentioned effects would seem to be, at least in part, reflections of changes in the condition of the smallest blood vessels. The experiments reported in this paper are attempts to determine directly the character and extent of changes in the cutaneous blood vessels following administration of certain steroids to castrate, eunuchoid, and normal men.

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METHODS AND PROCEDURES

The present studies are based primarily upon two new methods for testing the sensitivity of the smallest cutaneous blood vessels to graded stimulation. One method, already employed in measuring the irritability (vasoconstriction) of blood vessels in normal subjects (8), tests the sensitivity of cutaneous blood vessels to various intensities of mechanical stimulation. The intensity of stimulation can be accurately controlled and varied at will with regard to either the rate or the force of application.

The second method rests upon a quantitative measure of the time required for a period of local ischemia to elicit a given degree of reactive hyperemia. This response is the result of the production within the tissues of vasodilating substances. The normal range of individual and seasonal values (9) offers a basis for comparison with the vascular actions of the steroid hormones. Details of the routine in these and in the other tests employed are as follows.

Each subject came to the laboratory in the early afternoon. After a period of relative quiet, observations were begun. First, the threshold time for production of a given degree of reactive hyperemia was measured.

This was followed by determination of the intensity-duration curve for the excitation of capillary contractility. This consists of measuring on the inner aspect of the forearm the minimal weight necessary at any given rate of application to evoke a light line of erythema along the

path followed by the automatically-driven contact point. The line of erythema appears in the center of an area of pallor (vasoconstriction). This threshold response, which may be determined to within 20 gm. or less in a total of from 200 to 1,000 gm. comprises the first two steps of the 'triple response' (10).

The next measure was of the effect of circulatory stasis on the above-described threshold to mechanical stroking. The procedure was designed to gauge the sensitivity of the contractile elements of the blood vessels to deprivation of oxygen; this method has been accorded extended study in an earlier paper on other subjects (8).

The third measurement was of changes in the skin temperature of the forehead, hands and lower leg. These were made with the patient in recumbent and standing positions in order to gauge vasomotor adjustments to postural changes (cf. 11).

On the following morning the subject returned to the laboratory for repetition of the determinations of the previous day. In addition, examination was made of the effect of iontophoretic passage into the skin of definite amounts of eserine sulfate. A fresh solution was prepared in a concentration of 0.1 mg. per cc. of distilled water and applied on a saturated cotton pad around a brass electrode (diameter of 1.9 cm.) which served as the anode. The current was 22.5 volts at 1 milliampere. The passage of the current continued 1 minute and in a few instances, for either 2 or 4 minutes. The extent and development of the pattern of erythema at intervals of five minutes denoted the sensitivity of the cutaneous blood vessels to the dilating action of eserine. The procedure was employed in an attempt to ascertain whether or not the hormones rendered the blood vessels more susceptible to a drug which sensitizes the tissue to the action of acetylcholine.

Tests of capillary fragility by the suction method were also made according to the technique of Brewer (12).

Immediately after completion of these procedures, the subject was prepared for injection of hormone. He was seated comfortably with one finger in a plethysmograph sealed with care to allow return of venous blood from the digit. A 30-gauge thermocouple junction of iron and constantin leading to a Leeds and Northrop (Micromax) recording potentiometer, was used to obtain a continuous record of the nail-bed temperature. When the droplet in the plethysmograph oscillated about a constant level with each heart beat, the injection of hormone was made intramuscularly in the contralateral upper arm. Room temperature and relative humidity were noted at intervals. The effects of the injection upon finger volume and skin temperature were thus observed for from one-half to a full hour. The data were plotted together on single coordinate paper. Upon completion of this procedure the tests employed prior to administration of hormone were repeated with notation as to the respective times since the injection. In some experiments, the more significant tests were repeated several times such as at 3 to 4, and 5 to 6 hours after the injection.

On the third day control readings were taken, the second injection given and the routine tests again repeated.

In contrast to the studies of castrate and eunuchoid men, the normal subjects were tested only on separate, rather than consecutive days.

The subjects used in this study included two castrate and two eunuchoid men who had been employed in an earlier spectrophotometric study of cutaneous blood vessels and their response to androgens (4). Other subjects included a normal man of 37 years, who was observed repeatedly in investigations of the effects of estrogen (13) and another normal man 26 years of age.

Tests were made before and after administrations of various hormones:[3] *a*), testosterone propionate (20 mg. per injection) in 13 instances, twice in normal subjects, twice in eunuchoids and nine times in castrates; *b*), desoxycorticosterone acetate (5 mg. per injection) once in a normal subject and twice in two castrates; *c*), progesterone (5 mg. per injection) once each in normal and castrate subjects; *d*), estradiol monopropionate (2.5 mg. per injection) once in a normal subject (who had been observed upon receiving six such injections in the earlier study (13)), and twice in two castrates. One cc. of peanut oil was used as the vehicle for all of the hormones. Control experiments included injections of this solvent alone twice into a normal subject and three times into two castrates. The type of material injected, i.e., hormone or blank injection was not disclosed to the subjects. Studies extended from December, 1940 to June, 1941.

RESULTS

Findings in Untreated Castrate and Eunuchoid Men That Did Not Differ Notably from Those in Normal Men

The capacity of the blood vessels to dilate and contract, as tested by local ischemia, was not unlike that in a large group of normal subjects. The seasonal trend (cf. 9) and ease with which reactive hyperemia is elicitable was in all four cases within the standard deviation of a group of 100 normal individuals.

Susceptibility of the blood vessels to graded mechanical stimulation (white reaction) was within the normal range, the average of the Lassalle coefficient in castrates being 0.85×10^{-4} and 0.82×10^{-4} respectively (see below for a description of the Lassalle coefficient of excitability). In the earlier study of 38 normal men, the mean coefficient was 0.53×10^{-4} with a standard error of the mean of ± 0.08. Thus the data for the two castrates fall outside the significant mean value for normal subjects, but in view of the paucity of data and the fact that they are obtained from only two subjects, the conclusion is not warranted that the smallest cutaneous vessels of male castrates are more excitable than those of normal individuals.

In one respect, however, the susceptibility of the

[3] The testosterone propionate (Perandren), desoxycorticosterone acetate (Percorten) and progesterone (Lutocyclin) were furnished by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

blood vessels to stimulation differed in castrate subjects from those in normal men. Their variability in reaction and 'spontaneous' instability are much greater than have been observed in any normal subject. Thus, in the normal man who has been studied most extensively, the coefficient of excitability has shown about a tenfold variation over a period of nine months, whereas the castrates have shown as much as a fifty-fold variation, within the space of three days. This variability could not be correlated with any particular event or condition.

The eunuchoid subjects had Lassalle coefficients of 0.19×10^{-4} and 0.29×10^{-4} respectively, and so exhibited lesser excitability of the blood vessels to mechanical stimulation than did the castrate men. In spectrophotometric studies (4) various values in eunuchoid men differed from those in castrate subjects. The limited character of the data, since it involves only a few men, allows only the suggestion that these differences between eunuchoid and castrate subjects are real.

Phenomena Not Affected by the Hormones Under the Conditions Employed

Other of the tests gave results that were consistently negative or were unaffected in any consistent

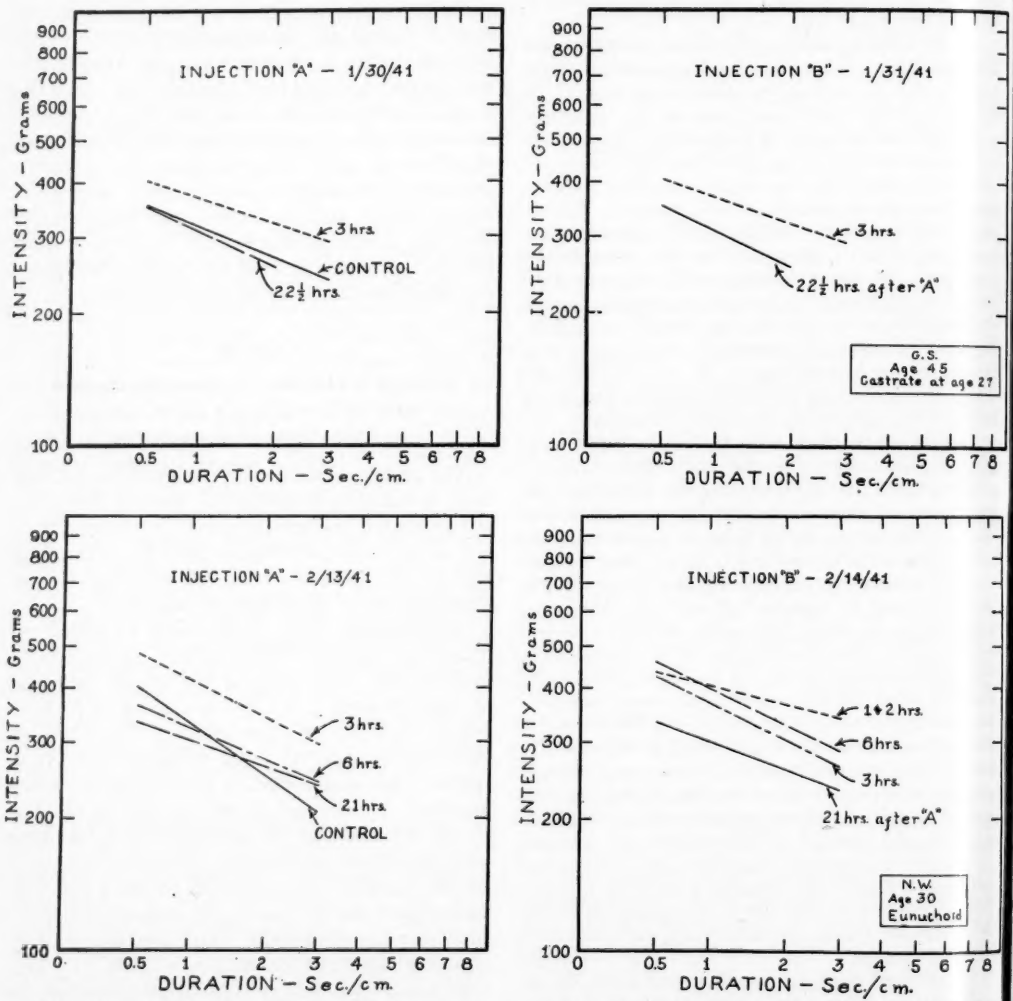

Fig. 1. Capillary constriction of skin blood vessels in response to graded mechanical stimulation. Plotted on logarithm-logarithm coordinates, shows that by 1 to 3 hours after injection of testosterone propionate more weight is required to evoke a threshold response, i.e., the excitability of the blood vessels is diminished. The upper set of curves are of the effects in a castrate man on 2 different days, the lower set are from a eunuchoid subject.

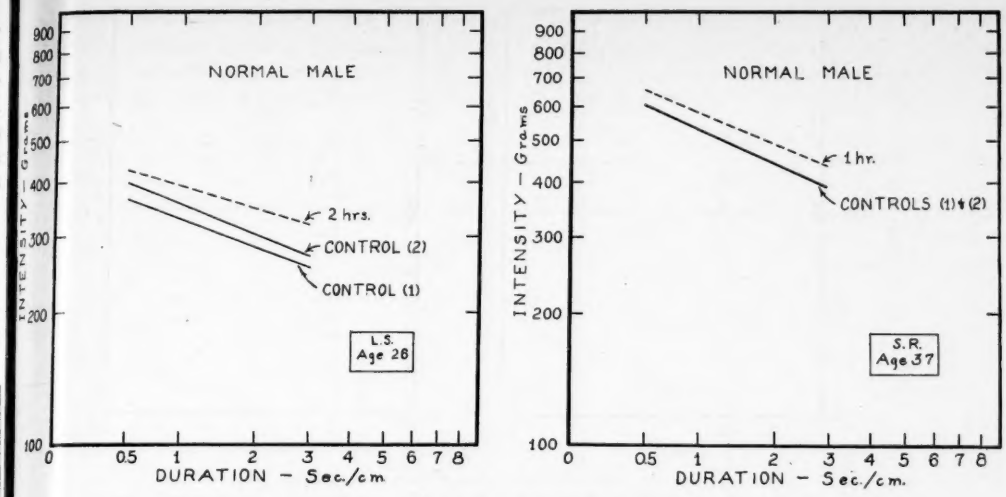

Fig. 2. Testosterone propionate causes a decrease in excitability of blood vessels in normal subjects. This can be compared with figure 1 of castrate and eunuchoid subjects.

manner by injected hormones. These included the adjustment of skin temperature to postural change, the response of the cutaneous blood vessels to ischemia (reactive hyperemia test), the sensitivity to eserine, and the fragility of the capillaries. Thus it is clear that arteriolar tone and its adjustment to change in position of the body is unaffected, at least within the first few hours, by any of the hormones used. Similarly, there is no altered susceptibility of the smallest cutaneous blood vessels to vasodilating substances, either as produced autogenously from local ischemia or as afforded in the introduction of eserine by iontophoresis.

Changes Induced or Influenced by the Hormones as Employed

Contractility of capillaries. The contractile response of cutaneous vessels upon graded mechanical stimulation is influenced by certain of the steroid hormones. Testosterone propionate raises the threshold of contractile response to mechanical stimulation, not only in castrate and eunuchoid but also in normal men. Exemplary changes are shown in figures 1 and 2 in which the logarithm-logarithm plotting of the intensity-duration curves are given prior to each injection (marked 'control') and at selected times after administration of the hormone. Vertical increases in the position of the curves after injection of the subjects show the minimal additional weight necessary at each speed of application in order to elicit a threshold response.

The coefficient of excitability (Lassalle coefficient = $\frac{1}{\text{rheobase}^2 \times \text{chronaxie}}$) shows a similar relationship in the direction of decreased excitability. In figure 3 and in subsequent graphs in which this value is indicated, the coefficient has been calculated, and any change in response after the injection is estimated in terms of percentage of deviation from the control value of the coefficient of excitability (8).

In general, these and other data show that during the first four hours following injection of testosterone propionate, there is a decrease in sensitivity (an increased threshold) for about four hours, but that by the sixth hour the excitability has returned to normal or greater than normal values, and so persists for as long as the measurements were continued (about 22 hours after injection).

As a point of correlation it is of interest to note in spectrophotometric evaluation of cutaneous vascular changes in castrate and eunuchoid subjects, that beginning within one hour after injection of testosterone propionate, there is an increase in the amount of oxygenated hemoglobin in the dermal vessels. "The action of male hormone began within one hour after injection, reaching a maximum effect in 2 to 3 hours" (4).

With injections of peanut oil alone, no regular change was observed in the excitability of the smallest blood vessels. In two tests of a normal subject, the oil was without measurable effect (fig. 4). In castrates some of the readings gave essentially control values, but there were instances, in keeping with the general observation of variable dermovascular irritability in these subjects, when there was considerable deviation from the pre-injection level, in the direction of increased excitability of the blood vessels (fig. 3). This erratic variability is in contrast to the consistent elevation of threshold (decrease in excitability)

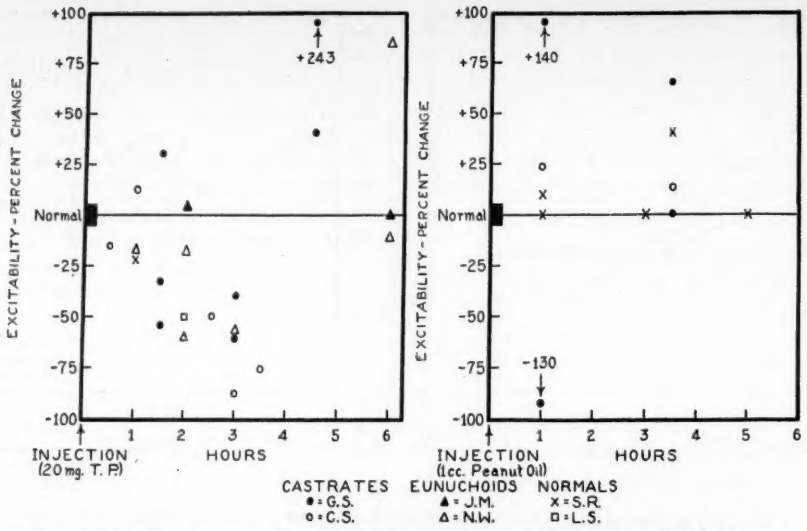

Fig. 3. COMPARISON OF EFFECTS IN THE SAME INDIVIDUALS OF TESTOSTERONE PROPIONATE (*left chart*) AND OF PEANUT OIL (*right chart*) ON THE EXCITABILITY OF DERMAL BLOOD VESSELS IN NORMAL, EUNUCHOID AND CASTRATE MEN. In the second chart, coefficients of excitability, calculated from the data of the intensity-duration curve observed in each man (see text), are compared in terms of percentage deviation from the control coefficient of excitability, which is the value observed prior to treatment with hormone.

observed following administration of testosterone (fig. 1, 2), and to the opposite effect of estradiol propionate, as described below.

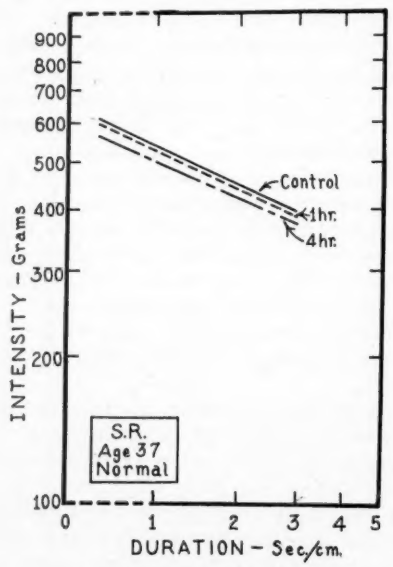

Fig. 4. EFFECT OF INJECTIONS OF PEANUT OIL. These exerted little influence on the intensity-duration curve of blood-vessel excitability in a normal man. In figure 3 is shown the variability in response of castrate men to mechanical stimuli, a variability not pronounced in the normal men under study.

The effect of the estradiol propionate is shown in figure 5. Whereas its influence as revealed in the logarithm-logarithm plotting was somewhat variable, the effect of the hormone as evaluated by the coefficient of excitability was consistent, namely an increased sensitivity of the blood vessels even in the normal subject whose vessels were unaffected by the injection of oil alone.[4]

With desoxycorticosterone acetate, however, no regular variation is seen in either manner of analysis of the data. This is shown in figure 6 in which the intensity-duration curve in *C.S.* was elevated markedly after one hour, whereas in *G.S.* and *S.R.* they were raised only slightly and the coefficients of excitability were even decreased at the end of one hour.

The effect of progesterone, in the two cases in which it was used, was quite similar in both normal

[4] The apparent paradox of little, or no change, in the effect of estrogen when the data are plotted on the double logarithm paper but of regular change in the coefficient of excitability, lies in the fact that the coordinate plotting focuses attention upon the intensity parameter of the strength-duration curve through the region of inflection whereas the Lassalle coefficient encompasses the intensity parameter (rheobase) at one extreme of the curve and the time parameter at the other (chronaxie). Thus, the rheobase may become elevated, and so the intensity elevated in the logarithm-logarithm plotting, and the chronaxie shortened, as in the case with estrogens. In such a case, the coefficient may change in one direction and the graph show no change, or even an opposite one. Since both methods of treatment are wholly empirical (8) one feels doubly reassured when both vary in the same direction, as with testosterone propionate, although the effect of a procedure probably may be estimated when (as with estrogen) the findings with one method of evaluation are consistent, and not wholly offset or contravened by the other.

and castrate men. Within the first hour the curves of threshold responsiveness were elevated and the coefficient of excitability was lower (fig. 7). By the fourth hour the values of the coefficient were in the reverse direction, indicating increased sensitivity of the blood vessels to mechanical stimulation.

All in all, therefore, testosterone propionate served to diminish capillary excitability during the first four hours; progesterone to diminish the sensitivity, but more transiently (perhaps related to the use of an unesterified compound); estradiol propionate apparently served to increase the excitability of the vessels; desoxycorticosterone acetate to be without a regular or well-defined action in either direction.

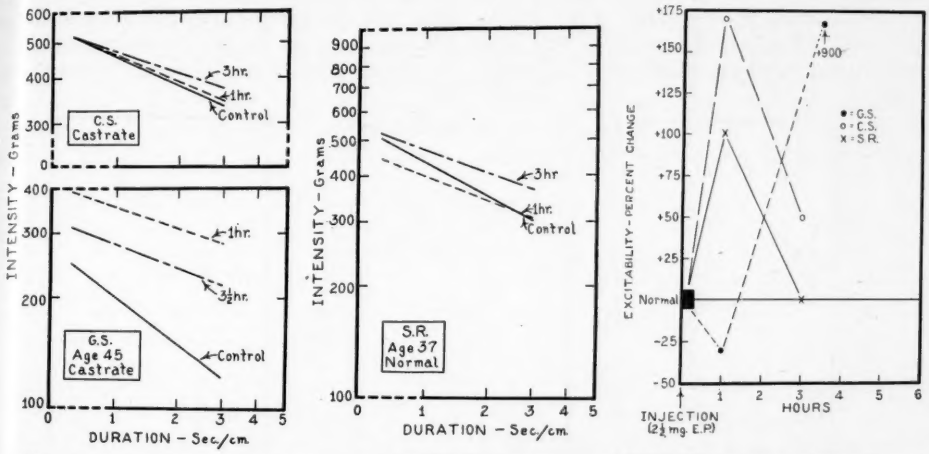

Fig. 5. Effects of estradiol propionate on excitability of blood vessels in castrate and normal men. These appear to be variable when listed in logarithm-logarithm plottings of intensity-duration curves (*left* and *center charts*), but when analyzed as changes in the coefficients of excitability (*right chart*), show an increased sensitivity of the blood vessels. In G.S., the 'control' curve occupied the lowest position ever obtained on any subject, as seen in comparison with control curves on the same subject at other times (fig. 1, 6). A footnote is appended to the text concerning fluctuations in blood vessel excitability in castrate subjects.

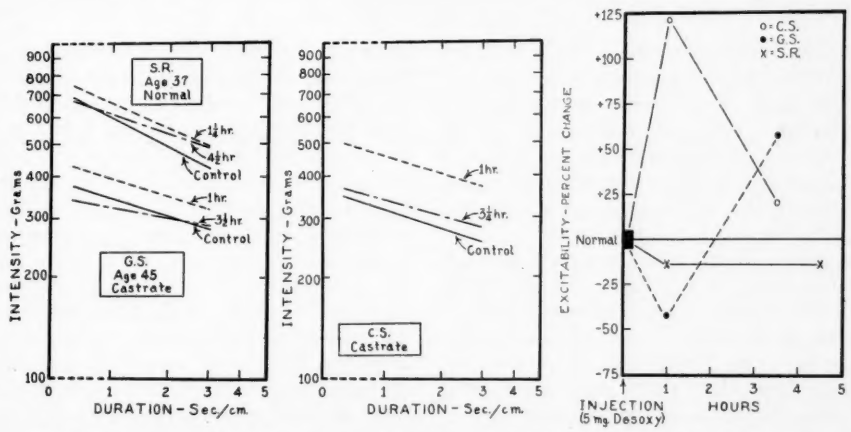

Fig. 6. Effect of administration of desoxycorticosterone acetate to one normal and two castrate men. The substance exerted no regular influence on the threshold (*left* and *center charts* of intensity-duration curves in logarithm-logarithm plotting) or coefficient (*right chart*) of excitability.

Susceptibility of blood vessels to ischemia. The sensitivity of the dermal blood vessels to ischemia was not observed to change in the two normal subjects with any of the hormones used, but underwent change in men with testicular insufficiency upon use of 3 of the steroid substances employed. In castrate

and eunuchoid subjects the threshold to mechanical stimulation upon circulatory stasis was altered as follows. In 6 of 9 tests in castrates and 2 of 4 tests in eunuchoid subjects, the threshold was raised, that is, the vessels were less excitable by testosterone propionate; with desoxycorticosterone acetate it was elevated 2 or 3 times in castrate subjects; with progesterone it was raised in a single test in a castrate

the dermovascular actions of estradiol propionate and testosterone propionate, although it must be recognized that the latter compound was employed in quantities eight times greater by weight than that of the estradiol propionate. Use of these larger quantities is in keeping with the employment of clinically effective doses. In the present observations the increase in finger volume following administration of

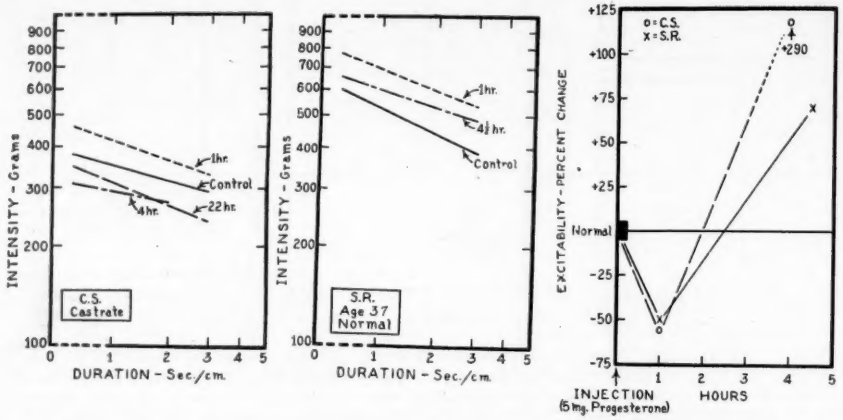

Fig. 7. ADMINISTRATION OF PROGESTERONE TO A NORMAL AND TO A CASTRATE MAN. This was followed within an hour by an increased threshold of excitability (*left* and *center charts* of intensity-duration curves with logarithm-logarithm plotting) and lower coefficients of excitability (*right chart*).

man. Estrogen had no measurable effect on blood vessel excitability following stasis in normal or hypogonadal individuals. These results signify, therefore, that the responses of the smallest blood vessels of the skin in castrate and eunuchoid subjects are affected by these hormones, testosterone propionate in particular rendering the vessels less susceptible to oxygen-lack, resulting from circulatory stasis.

Finger volume. Testosterone propionate gave rise in several instances to significant increases in the finger volume of castrate men. This was observed in 3 of 4 tests, with changes in volume ranging from 0.72 to 4.9 per cent. These values compare in magnitude with those which follow injections of estrogens in normal men and in menopausal women.

No effect on finger volume was observed with the use of estradiol propionate, progesterone or desoxycorticosterone acetate; this in marked contrast to the appreciable increase in volume induced by estrogen in normal men (13) and menopausal women (2). Estradiol propionate as well as desoxycorticosterone acetate, progesterone, and peanut oil were without effect in all tests in eunuchoid and castrate subjects. The oil vehicle either with or without testosterone propionate exerted no appreciable effect in the normal subject.

There appear to be important differences between testosterone propionate was accompanied in some instances by an appreciable elevation of skin temperature. This is the result of an increase in the rate of blood flow through the skin, and is in part presumably a reflection of relaxed tone in the dermal vessels, probably of the arterioles. With estrogen, however, the cases observed in a previous study (13) had an increase in finger volume unaccompanied by a change of skin temperature. When such a response to estrogen occurs, therefore, it may be the result of increase in fluid outside of the blood vessels (14) or of dilatation of the smallest vessels beyond the terminal arterioles. This latter possibility is supported by direct observation of the dilating effect of estrogen upon the blood vessels of the ear to castrated rabbits (5). Unpublished data (Edwards and co-workers) obtained by spectrophotometric study show, moreover, that injection of estradiol propionate (2.5 mg.) into two castrate men failed to give the large increase in the quantity of hemoglobin and shift to oxyhemoglobin observed upon injection of these same men with testosterone propionate (20 mg.). Thus there appear to be fundamentally different vascular actions of androgens and estrogens, differences that are demonstrable with respect to their sites of action, the nature of gonadal insufficiency at the time of injection, and the effects on the susceptibility of the

smallest blood vessels to trauma and circulatory stasis.

DISCUSSION

Little need be said regarding the results of this study, recapitulated in table 1. Of all the data, there is one prominent feature which should be of most general interest. It pertains to three related facts. *a*). In hypogonadal men, especially castrates, great instability of the cutaneous vessels is encountered. This is so clinically, and we have found this to be associated with transient and extensive increases in excitability to direct mechanical stimulation. *b*). A result of androgen administration is to increase the amount of oxyhemoglobin in the cutaneous blood vessels of hypogonadal men, especially castrates. *c*). And the smallest blood vessels in the skin of hypogonadal men are less excitable to mechanical stimuli during local anoxia after injection of androgen than before; this was the case with three of the four steroids employed (all but estradiol). The inferences to be derived from this association of facts are several. They suggest that the primary deficiency in hypogonadal men stems from the fact that the smallest blood vessels are denied an optimal complement of oxygen, in the form of oxyhemoglobin; they manifest this lack by vasomotor instability and ready susceptibility to further oxygen-lack. By analogy, therefore, the dermovascular action of androgens (and related substances) may mean that alleviation of vasomotor instability in hypogonadal males depends largely, if not primarily, upon augmentation of the available oxygen supply. Estrogen lacks this particular pharmacodynamic action which androgens clearly possess in hypogonadal men.

In conclusion, one further correlation may be made. Only estradiol of the steroids tested, failed to affect the excitability of the smallest blood vessels in the skin during local anoxia. One naturally asks how it differs from the others, stereochemically, or conversely, what the other three steroids have in common, in this respect. One common feature which these three molecules with similar actions possess is that they are alpha, beta unsaturated ketones, with the carbonyl group in position 3 and the alpha carbon at Δ^4. The fact that testosterone was so much more effective than the other substances in the present experiments may best be explained on the grounds that it was used in much higher dosage than were progesterone and desoxycorticosterone acetate.

The intriguing question remains for future investigation, therefore, as to why this particular chemical moiety in ring I of a steroid substance evokes this specifically demonstrable action.

TABLE 1. TESTS OF DERMOVASCULAR ACTIONS OF STEROID HORMONES

Hormone Used	Vasodilation of Smallest Vessels		Vasoconstriction of Vessels		Fragility of Capillaries, (suction)	Finger Volume Change After Injection (plethysmograph)	Susceptibility of Capillaries to Lack of Oxygen	Types of Subjects
	Reactive hyperemia	Eserine by iontophoresis	Excitability, (capillary constriction)	Arteriolar adjustments, (with change in posture)				
Testosterone propionate	o	o	−	o	o	+	−	Castrate
	o	o	−	o	o		−	Eunuchoid
	o	o	−	o	o	o	o	Normal
Progesterone	o	o	−	o	o	o	−	Castrate
	o	o	−	o	o	o	o	Normal
Estradiol propionate	o	o	+	o	o	o	o	Castrate
	o	o	+	o	o	+	o	Normal
Desoxycorticosterone acetate	o	o	o	o	o	+	−	Castrate
	o	o	o	o	o	o	o	Normal
Peanut oil	o	o	o−+	o	o	o	o	Castrate
	o	o	o	o	o	o	o	Normal

SUMMARY

Upon two castrates, two eunuchoid and two normal men repeated measurements were made of a number of cutaneous vascular and vasomotor adjustments following single injections of certain steroid hormones, and of the peanut oil vehicle alone. The hormones employed were testosterone propionate, estradiol propionate, progesterone, and desoxycorticosterone acetate.

Some of the tests reflected no difference between normal and hypogonadal men. These tests included *a*), the contractile response of the blood vessels upon graded chemical stimulation of the integument; *b*), the vasomotor adjustment of dermal blood vessels to postural changes; *c*), the ease with which reactive

hyperemia was induced by local ischemia; *d*), the effects produced by eserine, as introduced by iontophoresis; and *e*), capillary fragility. In all of these respects the responses of dermal blood vessels of castrates and eunuchoids did not definitely exceed normal limits.

The excitability of the cutaneous blood vessels as measured by graded mechanical stimulation was far more variable in castrate than in normal men. The variations were characterized by the suddenness of their appearance and by their extensiveness.

Two of the hormones rendered blood vessels less excitable in all subjects tested. Testosterone propionate had the most marked effect which reached a maximum about the fourth hour following the injection. Progesterone had a similar action, but less marked and more transient. Desoxycorticosterone acetate exerted no consistent influence. The excitability of the blood vessels in all subjects was increased slightly and in a transitory fashion by estradiol propionate. A summary of these results is given in table 1.

In individuals with testicular insufficiency, more than in normal men, all of the steroids under trial, except estradiol propionate, increased the threshold of the susceptibility of blood vessels to deprivation of oxygen. The deprivation of oxygen was obtained by complete circulatory stasis from a ligature applied to the arm.

Testosterone propionate caused a marked increase in the finger volume of castrate men. This action was not seen in the normal or in the eunuchoid men. Desoxycorticosterone acetate, progesterone, and estradiol propionate exerted no detected effects on finger volume in castrate or in eunuchoid individuals. Only estradiol propionate increased finger volume in the normal men.

CONCLUSIONS

Significant differences exist between the dermovascular actions of estrogen and testosterone propionate. Androgens and estrogens exert demonstrably different effects upon the blood vessels of the skin. The reactions, in part at least, apparently affect different regions of the vascular tree, and depend also upon the degree of gonadal insufficiency at the time of injection. In castrated males, there are fluctuations in excitability of the smallest blood vessels of the skin which greatly exceed those found in normal subjects. These fluctuations not only exceed by a wide margin the relatively small changes in excitability noted in normal men, but are also characterized by suddenness of appearance and disappearance as well. Finally, correlations made with previous spectrophotometric studies (4) of blood in cutaneous vessels show the increase of hemoglobin in the skin after injection of testosterone to be coupled with transient vasodilatation and diminished excitability of the smallest blood vessels of the skin.

REFERENCES

1. REYNOLDS, S. R. M., AND F. I. FOSTER: *Am. J. Physiol.* 128: 147. 1939.
2. REYNOLDS, S. R. M., S. KAMINESTER, F. I. FOSTER AND S. SCHLOSS: *Am. J. Obst. & Gynec.* 41: 1022. 1941.
3. REYNOLDS, S. R. M., S. KAMINESTER, F. I. FOSTER AND S. SCHLOSS: *Surg., Gynec. & Obst.* 73: 206. 1941.
4. EDWARDS, E. A., J. B. HAMILTON, S. Q. DUNTLEY AND G. HUBERT: *Endocrinology* 28: 119. 1941.
5. REYNOLDS, S. R. M., AND F. I. FOSTER: *J. Pharmacol. & Exper. Therap.* 68: 173. 1940.
6. REYNOLDS, S. R. M.: *J. Physiol.* 95: 258. 1939.
7. REYNOLDS, S. R. M., AND F. I. FOSTER: *Am. J. Physiol.* 131: 422. 1940.
8. DI PALMA, J. R., S. R. M. REYNOLDS AND F. I. FOSTER: *J. Clin. Investigation* 20: 333. 1941.
9. DI PALMA, J. R., S. R. M. REYNOLDS AND F. I. FOSTER: *Am. Heart J.* 23: 377. 1942.
10. LEWIS, T.: The Blood Vessels of the Human Skin and Their Reactions. Shaw & Sons, London, 1927.
11. MAYERSON, H. S., AND L. A. TOTH: *Am. J. Physiol.* 125: 474. 1939.
12. BREWER, J. I.: *Am. J. Obst. & Gynec.* 36: 597. 1938.
13. REYNOLDS, S. R. M., AND F. I. FOSTER: *J. Clin. Investigation* 18: 649. 1939.
14. FREED, S. C., AND E. LINDNER: *Am. J. Physiol.* 134: 258. 1941.

Clinical Use of Testosterone in the Male Climacteric

[Testosterone Therapy]

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THE MALE CLIMACTERIC presents one of the complex problems of aging. Its etiology is confused and undetermined. Its symptomatology is involved, tremendously varied, and rarely brought to the attention of the physician in all its diversity. This latter fact is so, because of the very diversity of these symptoms and because of the apparent lack of relationship between the various physiologic systems involved. Treatment of this state is still in its earliest trial stage.

No definite set of criteria for determining the age limits of the climacteric state has been developed. Limits range from Havelock Ellis' description of the onset of the 'critical age' at 38, to any decade thereafter. Certainly, copulatory frequency is no criterion of the climacteric since Pearl's data on such frequency indicated a high variability—8 to 10 times as variable as data for body weight. And although, according to Engle (1), sex impotence is a concomitant of the aging process, the variability of this symptom is too great to permit its use as a sole criterion. Moore (2) believes that old age as determined by the morphology of the prostate may be considered definite at sixty years. However, only 4 of every 10 males showing such definite morphological changes of the prostate will show any signs of obstruction. The signs and symptoms of prostatism *per se*, therefore, cannot serve as criteria in determining the presence of the male climacteric.

From a hormonal point of view, additional difficulties present themselves. No phenomenon equivalent to the female menopause can be demonstrated in the male. There is no sharp decline in reproductive capacity within any one limited period. Nor is there, at any given time, a marked increase in the excretion of gonadotropins such as is demonstrable in women.

The menopause is one of the many signs of the aging of the female genital organs. Strictly speaking, the menopause means the final cessation of menstruation. Before this takes place, irregularities in menstrual rhythm and a whole group of neurocirculatory symptoms appear. These symptoms plus added psychic phenomena may persist for several years after complete cessation of menstruation. The term climacteric is used to embrace not only the menopause, but the whole symptom complex occurring during this period.

It is in this sense that the term climacteric may be applied to the male—as a period in life. In the same sense, although we cannot use impotence or the symptoms of prostatism or neurocirculatory disturbances individually as criteria for establishing the definite presence of endocrine imbalance, the related presence of all or some of these symptoms in a patient are indicative that we may be dealing with the male climacteric.

The symptoms of the male climacteric can, therefore, be grouped under four clinical headings: *a*), Neurocirculatory, *b*), psychosexual, *c*), genito-urinary and *d*), miscellaneous. The neurocirculatory symptoms include all those that may be observed in the female climacteric. These are hot and cold flashes, excessive perspiration, palpitation, dizziness, tingling, headaches and cardiac angina.

Clinically, it is rare to find the various anxiety states and other mental disturbances dissociated from the presence of decreased libido and partial or complete impotence. For this reason, it would appear best to link these phenomena under one category—the psychosexual.

The genito-urinary symptoms of frequency, nocturia, dribbling, inability to start the urinary stream and occasional dysuria are almost invariably associated with changes in the prostate and seminal vesicles—particularly with benign prostatic hypertrophy.

Among the miscellaneous symptoms can be included muscular aches, fatigue not attributable to the cardiovascular and other systems and the accumulation of lower-trunk fat (3).

It has been established that the ovarian hormones are necessary to maintain the female reproductive organs in good physiologic state. In the female, estrogenic substances play an important part in maintaining the water balance and the vascularization of the genital tissues—factors which are of fundamental importance in the study of the causes of aging. A

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similar relationship exists between the testis and the male genital tissues. According to Engle, atrophy of the prostate and seminal vesicles occurs following castration in all mammals, including man. Senile involution or atrophy seems to depend on the complete absence of the testis hormone. This would offer no explanation for the preponderance of benign prostatic hypertrophy in the fifth and later decades. To explain this state, Zuckerman (4) and Laqueur (5) have posited an imbalance between androgens and estrogens—the decrease in androgen during the climacteric enabling uninhibited estrogenic substances to produce prostatic hypertrophy. It is interesting to find in this connection that in 1936, Zuckerman (4) experimentally produced prostatic hypertrophy in monkeys by injecting estrogenic hormones. On the other hand, Lower, Engle and McCullagh (6) believe that the testis hormones have a fraction which decreases the prostate size by inhibiting the pituitary. During the climacteric, when there is a decrease in androgens, this inhibiting influence would disappear permitting the prostate to hypertrophy. This substance was called 'inhibin' by these investigators. In any case, some relationship between the hormonal state in the climacteric and benign prostatic hypertrophy does appear to exist. Working on this assumption, numerous investigators, including among others Zuckerman and Greene (7), Cary (8), Dix (9), Douglas (10), Bolend (11), and Day (12), have been clinically able to relieve in varying degrees the symptoms of prostatism by the use of testosterone propionate.

It was inevitable that, following successful replacement therapy in castrates, eunuchoids and youthful hypogonads, attempts should be made to treat the impotence associated with the male climacteric. McCullagh (13), Dunn (14), Hamilton (15) and Douglas (10) have reported the successful restoration of potency in the male climacteric by the use of testosterone propionate. Psychic disturbances and changes in the general physical state provide too confusing a complication to permit adequate evaluation of these results. Carmichael and Noonan (16), who treated 18 impotent men with androgens and obtained good results in 7 considered these good results as psychological in origin.

In the female, estrogenic substances have been found to give symptomatic relief of a wide variety of neurocirculatory symptoms occurring in and about the time of the female menopause. Reynolds and Forbes (17), working with estrogens in males have been able to produce definite dilatation of the skin vessels, establishing the vascular effect of these substances. Using the hypotheses of Zuckerman (4) and Laqueur (5) concerning androgen and estrogen imbalance, at least a tentative explanation of the hot and cold flashes and excessive perspiration seen in the male climacteric can be offered. From a clinical point of view, however, Bonnell, Pritchett and Rardin (18) have attributed vasodilatory properties to both estrogenic and androgenic hormones. These workers treated 23 patients having cardiac disease. Of the 23, 18 were men. Of these 18, 5 received androgens alone, 11 were given estrogens and 2 received both androgens and estrogens. Complete relief was obtained in 4 of these men and good to excellent results in 13 of them. Fewer anginal attacks occurred and fatigue and dyspnea decreased. The results were essentially similar whether estrogens or androgens were used. Here too, whether we are dealing with the reestablishment of some endocrine balance, or direct substitution therapy, some relationship does seem to exist between various neurocirculatory disturbances and the hormonal state preponderantly found in the climacteric.

We feel convinced that there is an imbalance of internal secretion in those men presenting various combinations of the above described symptom groups. And, since we feel that this imbalance is analogous to that which is so successfully treated in women with estrogenic substances, we have selected the following eight cases and treated them with testosterone propionate[1] after being convinced that, in so far as the cardiovascular symptoms were concerned, there was no organic pathology present. The first of this series of cases was carefully followed and treated both on the wards of the Bronx Hospital and in the Endocrine Clinic of the Bronx Hospital. *Cases 2, 3, 4, 5* and 6 were selected from the private practice of one of us (S.F.G.), and the last two cases were selected from the private practice of the other (M.J.M.).

CASE REPORTS

Case 1. I.H., age 55 was admitted to the Bronx Hospital July 30, 1940, with complaints of attacks of precordial pain of 6 years' duration. His past history was negative except for tonsillectomy and appendectomy and a trace of sugar found in the urine in November, 1939. Six years prior to admission the patient began to develop recurrent, gripping, non-radiating precordial pain. These pains appeared at rest and without effort and had begun to occur more frequently in the 3 months prior to admission to the hospital. On July 26, 4 days before admission, the patient experienced a very severe attack lasting 1 hour. The pain was associated with dyspnea. In the next few days, repeated attacks of precordial pain, radiating down the right arm and occasionally down the

[1] Testosterone propionate (Oreton) used with the first 6 patients, was supplied by Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J. *Case 7* received oral methyl testosterone (Neo-Hombreol (M) tablets). The products used in *case 8* (Neo-Hombreol ampoules and Neo-Hombreol (M) tablets) were supplied by Dr. L. Pirk of Roche-Organon, Nutley, N. J.

left arm occurred. The patient complained of dyspnea with the slightest exertion. The only other complaints were referable to the genito-urinary tract. There was frequency of urination, 3 to 4 times during the day with no dysuria. There was no impotence.

On admission, the patient looked obese and not acutely ill in appearance. There was no dyspnea. Lips showed a suggesting of cyanosis. Pupils were equal and reactive. The thyroid was not palpable. The lungs were clear to percussion and auscultation. Heart sounds were muffled. The point of maximum intensity was in the sixth interspace in the midclavicular line. No apical impulse or thrill was palpable. He had regular sinus rhythm. Blood pressure was 110/70 mm. Hg. The physical findings on examination of the abdomen and extremities were negative.

Laboratory examination showed a negative urine with good concentration. Blood chemistry revealed glucose 104.7 mg. per cent, urea 14.7 mg. per cent, uric acid 3.5 mg. per cent, creatinine 1.03 mg. per cent. Hemoglobin was 110 per cent, red blood cells 5,100,000; white blood cells 10,400 with 65 per cent polymorphonuclear leucocytes. Sedimentation rate was increased. An electrocardiogram taken on the day after admission showed no evidence of myocardial disease. Roentgenograms of the spine revealed a hypertrophic osteoarthritis of the cervical and dorsal spine. Basal metabolic rate was minus 18.

The temperature of the patient was normal on admission and persisted normal throughout his stay. On admission, he was placed on 1/150 grain of nitroglycerine for pain. In spite of repeated use this failed to give any relief. In view of the essentially negative clinical findings and the probablity that we were dealing with the climacteric period and its varied complications, the patient was placed on 25 mg. of testosterone propionate, administered intramuscularly every other day. By the end of the second week he stated that he felt much improved and that he was able to walk around with very little pain and no shortness of breath.

Three weeks after his admission to the hospital, the patient was discharged improved and was referred to the Endocrine Clinic where injections of 25 mg. of testosterone propionate were continued 3 times a week. A second electrocardiogram taken in the clinic showed no evidence of myocardial damage. The patient continued well on treatment, his only complaints being slight anginal pain. At the end of 4 months of treatment, injections were reduced to twice weekly and one month later to once weekly. He continued ambulatory and improved for an additional two months and then he began to complain of increased dizziness, weakness and precordial pain. In order to determine the possible effect of a placebo on the patient, his injections were increased to twice weekly. However, ampoules of sesame oil were substituted for testosterone propionate. At the end of one month, because of persistence of marked complaints, placebo treatment was increased to 3 times weekly. Two weeks later he was complaining of marked weakness, dizziness, insomnia, and severe recurrent anginal pain. His basal metabolic rate at this time was minus 11. Therapy was now changed back to 25 mg. of testosterone propionate, injected 3 times weekly. At the end of one month he felt much stronger and complained much less of pain. Treatment 3 times a week was continued for another month and a basal metabolic rate taken at this point was minus 4. However, despite testosterone propionate, the patient began to complain once more of chest pain, fatigue and dizziness. All treatment was, therefore, discontinued and within 2 weeks he felt much worse than at the time of the stopping of treatment. Once again, instead of returning to testosterone propionate, the patient was placed on sesame oil injected 3 times a week. Although he thought he felt better after the first week of this placebo therapy, at the end of the second week he felt much worse. He complained of generalized muscular pains, severe precordial pressing and shortness of breath. He was kept on sesame oil, but failed to show improvement. Testosterone propionate therapy twice a week was, therefore, resumed a third time and once again clinical improvement was observed with marked symptomatic relief. This time, testosterone propionate therapy was maintained for two months and then discontinued. Throughout the time the patient was under treatment, nocturia 2 to 3 times and frequency 4 to 5 times persisted unchanged. At about the time when all treatment was discontinued, frequency and nocturia became more marked and dysuria associated with suprapubic pain developed. Cystoscopy revealed hypertrophy of the prostate and a papilloma of the bladder just behind the left ureteral orifice. Since fulguration of the papilloma, dysuria and suprapubic pain have disappeared and there is nocturia one time. The patient, in the meantime, is ambulatory and attending to his work.

Case 2. T.S., 63 years of age, in whom a diagnosis of angina pectoris sine dolore had been made 20 years previously, had weakness and precordial distress, but no definite pain. At one time the electrocardiogram revealed myocardial damage. Since then, he has had five or six attacks of angina pectoris and has been confined to bed for periods of from several days to several weeks. Following these seizures, repeated electrocardiograms were negative. At the time he was selected for treatment, he complained of precordial pain on exertion (occasionally while at rest). He had hematuria on one occasion, probably due to a ureteral calculus which was passed. Laboratory data were negative. His blood pressure was 140/90 to 150/90 mm. Hg. In July, 1939, while he still complained of general weakness and precordial pain, he was given testosterone propionate (3 injections a week, 25 mg. per injection), for 10 weeks. Following this he suffered a severe anginal attack and was bedridden for several weeks. Treatment was then resumed. For a period of 2 months he felt better, had no attacks, and was free from pain for the first time in many years. His blood pressure rose to 175/90 mm. Hg. while under treatment. When he suffered another attack, treatment was discontinued.

This patient has attacks as frequently as before therapy and has not responded to the treatment.

Case 3. A.G., a 65-year-old physician, had had typhoid and erysipelas many years ago. Otherwise he had never been ill. In July, 1930, he began to experience precordial discomfort at times. During that period his blood pressure, electrocardiogram, urine and other laboratory data

were negative. In 1937, after a heavy meal, he felt a sudden pressure in the precordium, and felt very weak and dizzy. He was given 1/100 grain of nitroglycerine and was relieved. There was no further trouble for some time. Then symptoms typical of angina pectoris began to return. At times he had arhythmia and extra systole. Nitroglycerine was used with good effect. At times 2 or 3 doses a day were taken. He could not walk more than 200 or 300 feet without taking nitroglycerine. He was very irritable, suffered from anorexia and intermittent claudication, especially while in bed. He also complained of general muscular aches and pains.

In 1939 he received several injections of testosterone propionate. After 3 injections the precordial pain became considerably less frequent and less severe. As treatment proceeded (2 injections a week), his bodily vigor increased and he could walk several blocks without any discomfort. The dosage of testosterone propionate was gradually decreased to 25 mg. once a week, then once in 2 weeks and then once in 6 weeks, to the present.

He now carries on his medical practice without any difficulty, having no dyspnea and very infrequent precordial pain. He uses no nitroglycerine, and receives 25 mg. of testosterone propionate once in 5 to 6 weeks. The leg pains have disappeared and he is very comfortable.

Case 4. S.A., a practicing dentist, 60 years of age. He had had pulmonary tuberculosis which was arrested 25 years ago. Every now and then he complained of weakness and gastric disturbance. He also had suffered from muscular pains in the legs. He was well preserved, weighing between 180 and 190 pounds. The findings upon physical examination, including an electrocardiogram, were negative.

In May, 1939, he complained of dizziness, irritability, inability to walk more than a block without experiencing cardiac pain, and the fact that he could not stand at work. His blood pressure was 150/75 mm. Hg, pulse 80, regular and of good quality, his cardiac sounds somewhat distant. The lungs were negative except for a healed lesion. The abdominal examination and all laboratory data were negative.

He was given testosterone propionate, 25 mg. 3 times a week at first, and later twice a week and improved considerably, so much, as a matter of fact, that he discontinued treatment for 6 weeks, whereupon, all of his symptoms returned. He then received for 3 months, once a week, 25 mg. of testosterone propionate. Treatment was stopped in the middle of 1940. Since then, there have been no complaints referable to his heart.

Case 5. N.G., a cutter by occupation, 66 years of age, had never had any serious illness. He had been under the routine observation of a physician for 10 years. His weight has always been between 146 and 152 pounds. His blood pressure ranged between 145/70 and 160/80 mm. Hg. The urine and blood examinations were negative.

In 1932 he began to complain of precordial pressure, irregular muscular pains, and restiveness. His heart was negative on physical examination.

In 1937 he complained of shortness of breath and precordial pressure. His blood pressure was 150/75 mm. Hg.

In January, 1939, he started to complain of more precordial pressure and dyspnea. He could not walk more than one block. His weight was 146 pounds, blood pressure 140/65 mm. Hg, heart negative. He was very irritable, cried easily and for no reason, and felt depressed. He could not walk without a cane.

In June, 1939, he was started on testosterone propionate therapy. 25 mg. 3 times a week. Within a short time he claimed that he felt much better and walked as much as a mile without any dyspnea or fatigue.

In May 1940, the patient returned complaining of repeated anginal attacks. He was given a series of injections of 25 mg. of testosterone propionate once a week for 3 months. During this period he worked only 3 days a week. He improved considerably and stopped complaining of pain. Since then, he has retired, lives in the country and takes care of a small garden. There are no complaints of pain or fatigue.

Case 6. H.S., business man, 61 years of age. His past history reveals a left nephrectomy in 1907 for calculus-pyonephrosis. There was a 3-year history of recurrent precordial pain, pressing in nature, occasionally radiating to the right or the left or to both shoulders. He had dyspnea with moderate exertion associated with marked afternoon fatigability, lassitude and dizziness. In recent months the patient had become increasingly despondent, feeling that everything was wrong with him. For a period of the last 6 months (fairly coincident with his depressive state) the patient had developed nocturia 3 to 4 times and frequency 6 to 7 times. The urinary stream was very narrow and the patient dribbled markedly, persistently soiling himself. There had been no erections for a period of about 4 years. Physical examination showed moderate obesity, marked arcus senilis. Heart sounds were good, point of maximum intensity was in the fifth interspace in the midclavicular line, blood pressure 140/80 mm. Hg. There was an umbilical hernia and the prostate was smooth, firm and moderately enlarged. Intravenous pyelogram revealed a negative right kidney and an enlarged prostate. An electrocardiogram showed no evidence of myocardial damage. This patient was started on 50 mg. of oral methyl testosterone daily (5 doses daily) and treatment was continued in this way for 3 months. After the first 6 weeks of treatment, the patient showed a marked general physical improvement. He stated that he was able to wait upon customers in his store throughout the day with very little fatigue. Although nocturia 2 times and frequency 4 to 5 times were present, dribbling and soiling of underclothes had disappeared. Attacks of precordial pressing pain occurred less frequently and could often be ignored by the patient when they did occur because of the decrease in intensity. Associated with these changes in his physical state, there was a gradual disappearance of his fits of depression. At present, although treatment has been discontinued for 2 months, the patient appears bright, is able to work without precordial pressing pain, dypsnea or fatigue. Nocturia one time persists. There is no dribbling or frequency.

Case 7. S.S., age 63, widower. His past history reveals that he suffered from frequency, nocturia, dribbling, and

a narrow urinary stream of 5 years' duration. Two years ago a pressing, precordial pain unrelated to exertion and non-radiating in character appeared. In June, 1939, because of the severity of his urinary symptoms, a two-stage prostatectomy was performed. The wound healed completely. However, nocturia 2 to 3 times, dribbling and soiling of clothes persisted following the operation and showed no signs of decrease. Six months after the operation, the patient began to complain of increasing fatigue, precordial pressing attacks lasting 10 to 20 minutes and occurring 2 to 3 times a day, and dyspnea associated with the precordial pressing. Despite the fact that the patient was constantly troubled by thoughts of sexual intercourse, he found that erections were incomplete at this time, or else that ejaculation occurred prematurely. Physical examination revealed no apparent cardiac enlargement. Heart sounds were good, pulse rate 76 and blood pressure 150/100 mm. Hg. Fluoroscopy showed no evidence of enlargement of the heart and an electrocardiogram showed no evidence of myocardial damage. There was a healed suprapubic wound. The prostatic bed showed no evidence of prostate tissue. Urine examination was negative except for a trace of sugar. Fasting blood sugar was 87 per cent. A gastric series taken on this patient was negative.

The patient was started on 10 mg. of oral methyl testosterone 5 times daily. This treatment was continued for 6 weeks. At the end of this time there was no apparent change in the patient's symptoms. Oral methyl testosterone was, therefore, discontinued and the patient was placed on 25 mg. of testosterone propionate, intramuscularly, 3 times weekly. At the end of 3 weeks of treatment, the patient showed improvement in both his cardiovascular and urinary symptoms. Dribbling disappeared, nocturia occurred 1 to 2 times. The cardiovascular change was much more marked. Fatigue and precordial pressing became so mild, that the patient began to consider seriously remarriage. However, during this initial period of 3 weeks, all erections disappeared, and the patient definitely associated this phenomenon with his treatment. Injections of 25 mg. of testosterone propionate were continued 3 times weekly. The patient continued to show a steady improvement in his physical state by his activity and marked decrease of cardiac and muscular complaints. Nocturia one time persisted. At the end of 7 weeks of injections, occasional erections recurred with completion of the sexual act. Injections were decreased to one time weekly and on this dosage the patient had been maintained to date in this improved state.

DISCUSSION

It will be noted that in all these cases, the patients to a greater or less degree, complained of an effort syndrome. Likewise, they all suffered from climacteric symptoms—weakness, muscular aches and pains, irritability, lachrymosity, and restlessness, as well. In no patient (with the exception of *case 2*), was there at any time evidence of myocardial disease as determined by the electrocardiogram. None of them had hypertension (with the same exception) or showed any nephritic changes. All of these symptoms are typical of the climacteric in women. Warner (19), in 1939, described two cases of what he considered climacteric in the male, both of whom not only had tachycardia, dyspnea, and palpitation, but also flushes. They were completely relieved by testosterone propionate. He reminds us that tachycardia, palpitation and dyspnea occurred in 69 per cent of 197 cases of female climacteric which he had studied. That symptom-complex, as a matter of fact, occurred 9th, in 21 symptoms of the female climacteric listed in order of their frequency.

Case 2 (*B.S.*), who at one time did show electrocardiographic evidence of myocardial damage, had in recent times had repeatedly negative electrocardiograms. Under treatment, he improved temporarily, but he did experience severe attacks while he was receiving testosterone propionate. He is, at present, getting these attacks as often as and severely as before. This case did not show any favorable result.

Case 4 (*S.A.*) is important for the reason that when the patient discontinued the treatment for 6 weeks, his symptoms returned, and when treatment for 6 weeks, his symptoms returned, and when treatment was resumed, the patient improved again. It might be said that the result was due to the psychic effect of the injections. If this is so, it is truly remarkable, since trained psychiatrists have attempted to treat patients in the climacteric with not nearly as signal a success.

Case 1 provides the best refutation of the assumption that we are dealing with the psychological influence of injections and treatment. Repeatedly placebos failed to produce the symptom relief that testosterone was able to give this patient.

In cases 7 and 8, although methyl testosterone orally was able to give satisfactory relief of the neurocirculatory symptoms of *case 7*, no apparent effect of this apparently potent oral preparation was observed in *case 8*. *Case 8* did respond satisfactorily, however, to testosterone propionate administered intramuscularly.

It is not our intention to place the responsibility for the symptom of angina pectoris in the male climacteric on the absence or presence of any single hormone. We do maintain that an endocrine imbalance is very likely responsible, just as it may be for the frequent peripheral vascular phenomena which may occur during the climacteric. Incidentally, reports of the benefits of testosterone propionate in many peripheral vascular conditions are becoming more frequent. It seems quite possible to us that intermittent claudication and angina pectoris are not far removed from each other in etiology, especially in respect to this age group.

We wish to urge the careful study of men from 50 to 65 years of age when they complain of vague and often apparently unrelated symptoms, for evidence of the climacteric, and a subsequent use of testosterone propionate, in an attempt to relieve their suffering.

SUMMARY

Seven cases of effort syndrome, considered by us as a complication of the climacteric and treated with testosterone propionate have been reported. Of these cases, 6 responded favorably, and one, which was a true cardiac, did not respond.

REFERENCES

1. Engle, E. T.: In Problems of Ageing. E. V. Cowdry, ed. Williams & Wilkins, Baltimore, 1939. P. 446.
2. Moore, R. A.: *Am. J. Path.* 12: 599. 1936.
3. Donald, H. R.: *Clin. J.* 67: 323. 1938.
4. Zuckerman, S.: *Lancet* 2: 1259. 1936.
5. Laqueur, E., K. David, E. Dengemanse and J. Freud: *Ztschr. f. physiol. Chem.* 233: 281. 1936.
6. Lower, E. E., W. J. Engel and D. R. McCullagh: *J. Urol.* 34: 670. 1935.
7. Zuckerman, S., and R. Greene: *Lancet* 2: 1433. 1936.
8. Cary, F. S.: *Illinois M. J.* 73: 486. 1938.
9. Dix, V. W.: *Brit. M. J.* 2: 362. 1938.
10. Douglas, R. J.: *J. Urol.* 45: 404. 1941.
11. Bolend, R.: *South. M. J.* 32: 154. 1939.
12. Day, R. V.: *J. Urol.* 41: 210. 1939.
13. McCullagh, E. P.: *J. Am. Med. Assoc.* 112: 1037. 1939.
14. Dunn, C. W.: *Delaware State M. J.* 11: 76. 1939.
15. Hamilton, J. B.: *Endocrinology* 21: 744. 1937.
16. Carmichael, H. R., and W. J. Noonan: *Am. J. Psychiat.* 97: 919. 1941.
17. Reynolds, S. R. M., and F. I. Foster: *J. Clin. Investigation* 18: 649. 1939.
18. Bonnell, R. W., C. P. Pritchett and T. E. Rardin: *Ohio State M. J.* 37: 513. 1941.
19. Werner, W. A.: *J. Am. Med. Assoc.* 112: 1441. 1939.

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Effect of Androgens on the Blood Count of Men

[Androgens and Blood Cells]

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EUNUCHOID PATIENTS treated actively with testosterone propionate or methyl testosterone[1] frequently develop a rather striking increase in energy and a plethoric appearance. The observation of such changes led us to make serial determinations of the erythrocyte, hemoglobin, hematocrit and leucocyte levels of the blood and to attempt to correlate such changes as might occur with the basal metabolism.

When it was realized that a distinct rise in red cell count and hemoglobin followed the use of androgens in certain cases, blood counts which previously had been made at random were also correlated with previous therapy where possible. These are included in *cases* 1 to 4.

The data reported here were obtained on 12 patients. The shift of blood count in one of these has been reported (1) previously (*case* 3). Of these 12, eight were eunuchoids without evidence of pituitary disease; two had signs of pituitary disorder, one dwarfism and one roentgenologic evidence of pituitary or suprasellar neoplasm; two were sexually mature males with impotence. Four of the 8 eunuchoids without evidence of pituitary disease had received testosterone propionate intramuscularly for periods of two to three years and methyl testosterone subsequently; four were treated with methyl testosterone for periods of four to eighteen months and had had no previous androgen therapy. The pituitary cases and the mature males were treated chiefly with methyl testosterone orally.

In the charts and tables, routine blood counts made in the laboratory are represented where only erythrocyte count and hemoglobin are given; special counts made in the hematology research laboratory are represented where erythrocyte count, hemoglobin and hematocrit readings are shown. A Haden-Hauser hemoglobinometer was used. The basal metabolic rates were calculated by the Boothby and Sandiford (2) modification of DuBois and DuBois standards. Two runs constituted one test.

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[1] The testosterone propionate (Oreton) and methyl testosterone (Oreton-M) used in these studies were supplied through the courtesy of Dr. Erwin Schwenk and Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.

RESULTS

The results are shown in the accompanying figures and tables. The data in figure 1 and tables 1, 2 and 3 show some long-term effects of testosterone propionate on the erythrocyte and hemoglobin levels, and their relation to the B.M.R. In all cases methyl testosterone therapy was employed during part of the period of observation. Figure 1 shows the effect of methyl testosterone on the blood of a patient already made relatively mature sexually by the use of testosterone propionate. Figures 2 and 3 illustrate the effects of methyl testosterone on untreated eunuchoids. The data in tables 8and 9 show erythrocyte, hemoglobin and hematocrit levels and B.M.R. changes in two sexually mature, functionally impotent males receiving methyl testosterone. The years of age shown in the charts refer to the present.

Case 1 (fig. 1) was 24 years of age in 1936. He had severe eunuchoidism which had followed bilateral testicular atrophy occurring after attempted orchidopexy at the age of 11 years. During 1937 and 1938 testosterone propionate had led to a degree of maturity approximating average normal for 18 or 19 years of age. A slight rise in blood count and B.M.R. occurred under testosterone propionate therapy and there is a suggestion of a fall upon withdrawal, but in neither blood count nor metabolic rate were the shifts pronounced enough to be definite. on the other hand, the rise in both blood count and metabolism in response to methyl testosterone was quite marked, and the changes are parallel insofar as the data show. The blood count had fallen after the hormone had been withheld for one month in 1941. The blood count on February 3rd showed 5.81 million erythrocytes, 107 per cent hemoglobin, hematocrit 50 cc. per 100. Therapy was discontinued on February 21 and on March 21 the count showed a blood count of 5.59 million red cells, 91 per cent hemoglobin, hematocrit 46 cc. per 100 cc.

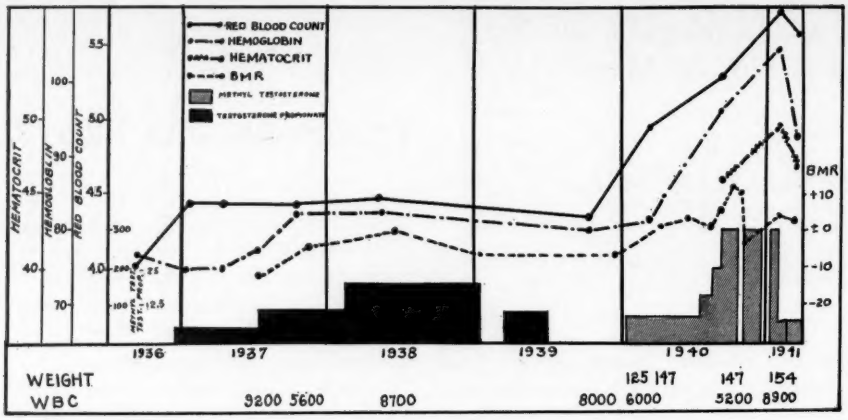

Fig. 1. Effect of androgens on blood count of eunuchoid, *case* 1, age 28.

There was no rise in leukocytes accompanying the rise in red cell numbers, and as the erythrocyte and hemoglobin levels increased the body weight also increased by 25 pounds, indicating that none of the rise in red cell count could be explained on a basis of blood concentration.

Case 2, (table 1), was one of severe eunuchoidism. Sexual maturation progressed strikingly on androgen therapy. There was a parallel rise of blood count and basal metabolism while he was receiving testosterone propionate. Under methyl testosterone therapy in 1940, the blood count and B.M.R. were considerably

Table 1. *Case* 2, eunuchoid, aged 33

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy	
							Test. Prop.	Methyl Test.
	lb.	million	%	cc./100 cc.		%	mg. per day	
12/17/36	162	4.50	78		8200	−24	5, begun	
3/ 1/37	165	4.60	80		7450	−13		
7/19	164	4.85	87			−15		
10/15		4.80	84		6100		25, begun	
5/ 5/38	171	5.00	83		5600	− 6		
12/ 6	170	5.16	91	43	6250	− 4		
3/ 1/39							Stopped,	
3/29							av. 10[2]	
1/ 2/40								Increasing
1/29								from 50 to 250
7/ 4								
8/15	166	5.70	97	49	9900	+13		Stopped
9/ 9	163	5.50	94	49	11000	− 9		
9/18						+ 4		250, begun
10/28						+16		Stopped
11/18						+ 7		300, begun
12/ 3	172	5.50	94	48	7750	+28		Stopped
12/20	170	5.50	91	46	8000	+ 2[1]		
1/10/41		5.34	87	43		−14		500, begun
1/21	161	5.36	91	47	8200			Stopped
1/27	160	5.26	87	45		+ 3		
1/30							25, begun	
2/14							50, begun	
2/17	170	5.36	87	45	8300	+ 7		
3/ 5	173	5.60	91	48	6950	+ 5		
7/ 1							Stopped	
7/24	180	5.05	84	44		+ 3	50, begun	
8/14						−13	100, begun	
9/ 8		5.40	91	48	7600	− 6		
12/—	193	5.83	94	53	6300			

[1] Basal determination on 12/12/40.
[2] In addition to two 200 mg. implants of testosterone propionate.

higher than under testosterone propionate. The blood count did not fall as rapidly as the metabolic rate on withdrawal of treatment in December, 1940. They were not raised appreciably by ten days of intensive methyl testosterone therapy in January, 1941. After an interval of ten days without treatment, testosterone propionate therapy produced a slight rise in blood count, which may represent some degree of summation.

In this as in other cases it will be seen that the weight rose with therapy while the blood count was rising and fell on withdrawal of therapy when the blood count fell. This would appear to exclude a concentration-dilution effect and to render the increase in blood count more significant. In this case an exception to the rule regarding weight shift occurs during the use of very high doses of androgens in January, 1941. This can be explained on the basis of the limited caloric intake which was imposed during a time when certain metabolic studies were being made. The white blood count suggests no concentration—dilution effect, being the same with low red counts in 1936 and 1937 as during high ones in 1940 and 1941.

In *case 2* during January, 1941, reticulocyte counts were made frequently, methyl testosterone in doses of 500 mg. per day orally being used from January 11 to 20th inclusive. The reticulocyte counts were as follows.

January	8	9	11	14	17	18	21	23	24	27
Reticulocytes, %	0.6	0.5	0.7	0.7	0.7	0.5	0.6	0.5	0.7	0.7

Case 3 (table 2). In this case severe hypogonadism followed mumps at 13 years of age. The androtin mentioned was an androgenic urinary extract of low potency. No change in blood count or B.M.R. accompanied its use. During 1938 while testosterone propionate was being used, the metabolic rate and blood count rose, the metabolic rate falling again after its withdrawal. It should be noted that in this case no blood count is recorded between November, 1938, and August, 1940. Testosterone propionate was discontinued in October, 1939, following which the B.M.R. fell to minus 29 per cent before the use of methyl testosterone was begun in February, 1940. The blood counts shown indicate no shift between 1938 and 1940, but in the light of the other data presented it seems reasonable to assume that a considerable fall in blood count occurred and was corrected again by August, 1940.

In 1940 a rise in metabolism of about 23 per cent accompanied the use of methyl testosterone and had not fallen in three weeks but did so within five weeks after cessation of therapy. A shift in hemoglobin and hematocrit levels is seen to accompany this reduction of the B.M.R. This case is of particular interest because the anemia had been shown to be persistent over a long period of time prior to effective androgen therapy in spite of the fact that iron medication, usually in the form of Blaud's mass or reduced iron in doses of 30 grains per day had been given during much of the time between 1933 and June 1, 1937. Since June, 1937 no iron medication or any other

TABLE 2. *Case* 3, EUNUCHOID, AGED 41

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy: Test. Prop.	Therapy: Methyl Test.
	lb.	million	%	cc./100 cc.		%	mg. per day (Androtin)	
March, '33	152	4.54	81	38	4950	−28		
August	150	4.01	71	34	5050			
June, '34		4.28	71	36	5100			
Dec., '35	166	4.40			7600	−27		
1937		4.20	72		6550			
3/ 1/38							25, begun	
7/20							50, begun	
9/20		5.04	84	46	6800		25, begun	
10/ 3	202					−18	50, begun	
11/30		5.00	94	46	8400			
12/ 6	198					−17		
2/ 8/39							25, begun	
10/10							Stopped	
2/23/40	194					−29		50, begun
3/27						−15		100, begun
8/ 7	207	5.30	94	48	6050	− 6		
9/24	203	5.30	91	49	5650	− 8		150, begun
11/12	200	5.60	100	51	6500	− 6		Stopped
12/ 3	192	5.10	91	44	5850	− 1		
12/16	190	5.00	94	42	5250	−22		60, begun
1/28/41								Stopped
4/ 2								50, begun
4/12	190	4.90	91	44		−13		
8/ 2		4.80	84	45	7700			

TABLE 3. *Case 4*, EUNUCHOID, AGED 35

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy	
							Test. Prop.	Methyl Test.
	lb.	million	%	cc./100 cc.		%	mg. per day	
12/24/36	140					−21		
4/15/37		3.90	78		5400		5, begun	
12/ 9							12.5, begun	
2/ 8/38		5.50	96		11200			
5/21	150					− 3		
7/30							25, begun	
4/15/39							Stopped	
7/19/40	146	4.20	81		4350	−20		
7/28	143					−28		200, begun
8/ 8	148					−13		
8/27	156					− 1		100, begun
9/14	168					+ 4		200, begun
10/12	175	5.10	95		5750	+12		300, begun
11/16	178	5.50	100		7050	+21		Stopped
1/14/41	165	5.40	91	46	4850	−10		60, begun
2/12								Stopped
2/27								100, begun
3/ 8	170	5.16	84	46		+10		
5/21								Stopped
5/24							25, begun 3×/wk.	
7/12		5.50	91	49				
9/13							50, begun, 3×/wk.	
9/27	173	5.58	97	50	6100		Stopped	

treatment directed toward the anemia had been employed.

Here as in other cases there was no shift in leukocyte count parallel to that seen in erythrocyte count and the weight tended to be higher during intensive androgen therapy and to increase with the blood count.

Case 4 (table 3) showed a well-marked rise and fall of both the metabolic rate and blood count in response to testosterone propionate, but the determinations are too few to be significant unless considered in conjunction with the changes in the preceding cases. Methyl testosterone had a similar effect, more marked in the B.M.R. curve. The determinations during early 1941 show a rise in the basal metabolism in response to resumption of methyl testosterone in smaller interrupted doses. An explanation of the lower blood count in the determination in March, 1941, is not obvious. It probably represents a fall toward average normal levels occurring gradually

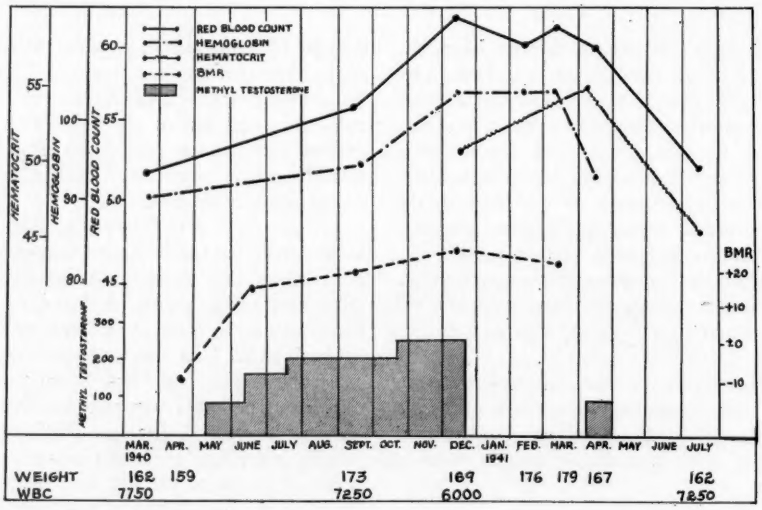

Fig. 2. EFFECT OF METHYL TESTOSTERONE ON BLOOD COUNT OF EUNUCHOID, *case* 5, AGE 21.

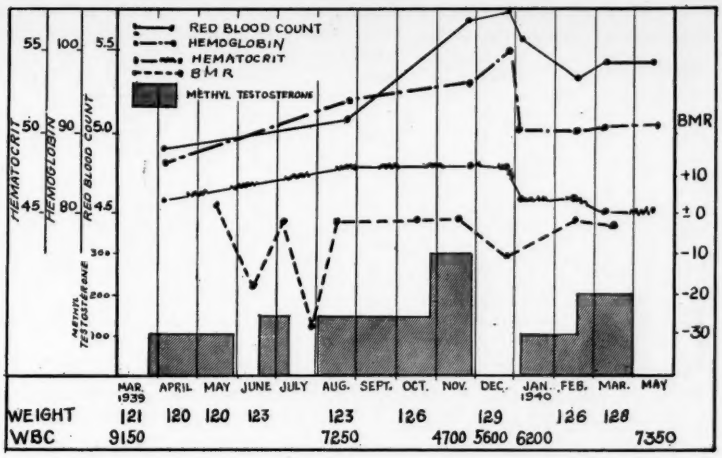

Fig. 3. Effect of methyl testosterone on blood count of eunuchoid, *case 6*, age 24.

after abandoning the very high doses of October, 1940, and earlier.

Case 5 (fig. 2) was a case of marked eunuchoidism of unknown origin without clinical or roentgenologic evidence of pituitary tumor. The well-defined response of the metabolic rate and blood counts to methyl testosterone therapy are shown. Here as in the other cases there is a rise in body weight paralleling that of erythrocyte numbers, and no significant shift in the number of leukocytes.

Case 6 (fig. 3). This is a case of moderately marked hypogonadism with no clearly defined cause and without clinical or roentgenologic evidence of pituitary tumor. He showed a well-defined response of the metabolism and blood counts to methyl testosterone therapy. On withdrawal of therapy in late November, 1940, the fall of blood count lagged behind that of B.M.R.; the basal rate fell within four weeks after the withdrawal of therapy, but the blood count did not fall until six weeks after withdrawal.

Case 7 (table 4). This man showed distinct evidence of hypogonadism. His nutrition was good; he lacked the relative pallor seen in the preceding cases; his body contour was relatively normal; his bone age was 17 years. Although both blood count and B.M.R. were not abnormal before treatment, both rose definitely during treatment. When his treatment was changed from methyl testosterone to testosterone propionate for two months, no shift in blood count or metabolic rate was seen.

Case 8 (table 5). Here the evidence of eunuchoidism was present without an accompanying anemia; no change in blood count occurred despite a definite change in B.M.R. in response to institution and withdrawal of methyl testosterone therapy. The dose was smaller than that in most of the other patients, but sufficient to produce rapid sexual maturation.

Table 4. *Case 7*, eunuchoid, aged 24

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy	
							Test. Prop.	Methyl Test.
	lb.	*million*	%	*cc./100 cc.*		%	*mg. per day*	
10/22/40	168	5.00	91	42	5200			100, begun
11/ 9		4.70	84	43	7400			Stopped
11/18	177					−10		70, begun
12/23	183					+11		60, begun
1/13/41	186	5.90	300	50	5200	+10	12.5	
2/10	187	5.80	94	48				
3/ 8	183	5.80	94	48		+ 9	Stopped	
3/31	177	5.70	94	48		+ 6		60, begun
5/12	186	5.60	91	50	1000	+ 9		
7/ 7	184	5.88	100	52		+24		
7/21		5.60	94	51	8700			100, begun
9/ 8	196	5.90	97	52	8300	+37		Stopped
9/23	181					− 1		

TABLE 5. *Case 8*, EUNUCHOID, AGED 19

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy Testosterone Propionate
	lb.	*million*	%	cc./100 cc.		%	*mg. per day*
10/ 9/40	145	5.15	97	44	4600	−15	100, begun
10/25	153					− 5	
11/ 6							Stopped
11/22	157					−13	100, begun
12/16	159	5.04	94	46	4350	+ 4	
1/24	167	5.14	94	46		+ 1	50, begun
3/ 5							Stopped
3/26	162	5.08	91	46		−12	
4/ 1							100, begun
6/30	163	5.19	87	46		− 5	

Hypogonadism of Pituitary Origin

Case 9 (table 6) was a pituitary dwarf and was growing rapidly in height during the period of methyl testosterone therapy, although he had grown very slowly previous to its use. A rise in blood count occurred following the use of methyl testosterone; however, the changes of erythrocytes, hemoglobin and hematocrit were not parallel, and thus appeared to reduce the significance of these changes, especially since no hematocrit level was obtained in 1939. The appearance of the patient himself, however, changed considerably during the treatment. In the beginning he had a sallow pallor such as is often seen in cases of pituitary deficiency, whereas after treatment his color was that of a healthy male and his ears which were previously rather white have become noticeably red. The B.M.R. appeared to show some rise on August 26, 1940 but this was not consistent, and on continued large doses was still minus 4 per cent on November 27, an insignificant change as compared to pre-treatment levels. Subsequent continuation of large doses failed to produce hypermetabolism. It can be seen that the low body weight of this patient indicates a much larger relative dose of androgens than was given in any of the other cases.

Case 10 (table 7). This case was one in which there was roentgenologic evidence of pituitary tumor without visible signs of optic nerve degeneration or visual field defect. He had the body contour of a eunuchoid but was of normal height. A rise in B.M.R. following the use of methyl testosterone was shown on one occasion but the shift in blood count is insignificant. No rise in hemoglobin levels occurred during two and one half months of methyl testosterone therapy.

It is interesting in these two cases of pituitary disease to speculate as to whether the pituitary insufficiency presumed to exist may have been a barrier to the production of such metabolic increases as have been seen in the other hypogonadal patients.

Patients without Hypogonadism

Of the two sexually mature cases, *case 11* (table 8) showed some rise in blood count which is not great enough to be significant, with a well-marked rise in

TABLE 6. *Case 9*, PITUITARY DWARF, AGE 20

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy Methyl Testosterone
	lb.	*million*	%	cc./100 cc.		%	*mg. per day*
4/18/39	65	4.45	78		7200	− 9	(Antophysin)
2/ 5/40							50, begun
3/ 6							100, begun
5/22	78					− 9	200, begun
8/26	80	4.80	84	42	5700	+ 5	Stopped
9/20	76	5.00	91	41	6300	−11	200, begun
10/14							300, begun
11/27	82	5.07	87	43	5850	− 4	Stopped
1/11/41	79	5.10	87	43	6950	−11	
2/ 1							60, begun
3/ 6		5.16	84	44			200, begun
5/19	89					− 9	
6/11		5.10	81	44	7400		
6/16							100, begun
6/22							Stopped
6/27							200, begun
10/25		5.37	91	46	7450		
10/31	91					− 1	

TABLE 7. *Case 10*, EUNUCHOID WITH PITUITARY TUMOR, AGED 20

Date	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy Test. Prop.	Therapy Methyl Test.
	million	%	cc./100 cc.		%	mg. per day	
10/29/40	4.18	78	37	3150	− 7		
2/ 1/41	4.30	78	38				
2/ 8					−11		
2/13							100, begun
3/ 1	4.30	78	38		− 5		200, begun
3/14	4.45	78	41		+7		
4/ 9	4.56	78	38	4600	+22		
5/ 5							Stopped
5/13					− 4		
5/24	4.53	78	41	4250			
5/31						50 begun	
7/ 9						Stopped[1]	
7/17							200, begun
8/30							Stopped
9/3							100, begun

[1] See note of 7/2 and 7/1

B.M.R. when methyl testosterone was given. *Case 12* (table 9) whose blood count was originally quite high, showed no definite change in blood count in response to therapy although a distinct rise in basal metabolism occurred.

TABLE 8. ARTERIAL HYPERTENSION, *Case 11*, AGED 62

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy Methyl Testosterone
	lb.	million	%	cc./100 cc.		%	mg. per day
8/20/40		4.3	84		9100		(bed rest)
9/20		4.5	81	40	4250	−18	
9/25	159					−18	100, begun
10/2	159					−18	250, begun
10/ 7	161	4.8	87	42	7450	− 2	
10/12						− 1	

DISCUSSION

Concerning the mechanism by which the sex difference in blood counts is brought about, several possible factors may be considered, among which are the following. (*a*) The effect of androgens upon the blood count may be related to the increase in metabolic rate (3–6) which is known to be produced by these steroids. Whether such an effect is produced by direct action of the androgens or is mediated by other organs, such as the pituitary for example, is not known. (*b*). The greater quantity of androgens in the male may have a direct effect upon the blood forming organs. (*c*). The difference might be due in some degree to genetic factors. (*d*). In the female, menstrual blood loss forms an additional factor in producing lower blood counts.

TABLE 9. *Case 12*, NORMAL SUBJECT, AGED 32 IN JUNE, 1941

Date	Weight	R.B.C.	Hemoglobin	Hematocrit	Leucocytes	B.M.R.	Therapy Test. Prop.	Therapy Methyl Test.
	lb.	million		cc./100 cc.		%	mg. per day	
11/20/40	153	6.14	111	56	9500	− 9	50, begun	
12/15	152					−13	Stopped	
2/26/41		6.22	108	55				100, begun
3/19	156	6.38	108	55	9850	− 5		
3/24								200, begun
4/ 8	161					−10		
5/15	165					+17		
5/28	163	6.10		52	100	+ 2		Stopped
8/29	157	6.01		53	104			

Menstrual blood loss is at most only a partial cause of the sex difference in blood counts, since this difference exists between man and postmenopausal women. Also, this difference is well-marked in birds

(7, 8). The fact that such a difference exists in both homozygous and heterozygous species argues against the genetic factor.

Shift in blood count during adolescence. That a distinct shift in blood count does occur during adolescence has been clearly shown by Williamson (9) in a study of hemoglobin levels in 919 individuals of all ages. He found a rise of about 1 gm. in hemoglobin level in both sexes in his 11 to 16-age-group. Such a rise was shown for hemoglobin, and for erythrocytes as well, in the same age group by Osgood and Baker (10). Williamson noted the first definite sex difference in hemoglobin levels in the 16 to 20-age-group, this difference continuing to the sixth decade.

Adolescent changes in production of 17-ketosteroids. The recently published study of Nathanson et al. shows that the urinary excretion of 17-ketosteroids is slightly greater in the male from the ages of 4 to 8 years. A sharp rise occurs in the male from the ages of 8 to 12 and an equally sharp rise of shorter duration in the female, from 9 to 11 years. The sex difference is well-marked after the age of 12, the average output in the female being 75 per cent of that of the male. It appears, therefore, that since a shift in the sex difference in both blood count and 17-ketosteroid production occurs at the same time of life, a causal relationship may exist.

The fact that injections of testosterone propionate or orally administered methyl testosterone raise the basal metabolic rate seems well established. Kenyon (3) found marked increases in cases of eunuchoidism treated with testosterone propionate over a period of months amounting to as much as 38 per cent increase. Thompson and Heckel (4) have reported a similar increase in a case of eunuchoidism. Rossmiller and I (5) reported ten cases of male hypogonadism treated with methyl testosterone showing increases in basal metabolism. The maximum rise in this group was 54 per cent; the average of maximum rises in the ten cases was 27.6 per cent.

Adolescent changes in B.M.R. Since it is known that there is a greater increase in 17-ketosteroid production in the male than the female following puberty and since it is known that some of the ketosteroids have the power to raise the basal metabolic rate, it would appear that some sex difference in B.M.R. could be correlated also with adolescence. Such a correlation however, does not appear to have been established and the literature contains some disagreement on this point.

Aub and DuBois (13) found an upward swing in the metabolic rate for prepuberal and puberal males at 12 years, the curve resuming its previous downward course at 14 years. In the data of Boothby and Sandiford (2) and Boothby, Dunn and Berkson (14) the sex difference in B.M.R. is greatest about the age of 18 years. This difference does not appear by their tables to be significantly greater, however, in adults than in children.

Relation of B.M.R. to the rise in blood count under androgen therapy. It is interesting that throughout these studies in those cases in which a blood count response was present, an increase in basal metabolism was also observed. In *cases 8* and *11* there was an increase in B.M.R. but no significant shift in blood count. Methyl testosterone in the doses used caused higher levels of the metabolic rate than followed the use of testosterone propionate and for the most part the highest points of metabolic rate in each case were associated with the highest blood counts.

In the three hypogonadal cases in which a response in blood count was least apparent (*cases 8*, 9 and 10), the rise in B.M.R. was less marked than in the others, the one high level shown in *case 10* being an exception. The average maximum increase in basal rate in the cases with a significant response in blood count approximated 38 per cent, while the average maximum increase in the cases which did not show a blood count response approximated only 22 per cent.

The question arises as to whether the rise in basal metabolic rate creates a demand upon the blood for greater oxygen carrying capacity which might result in an increased number of erythrocytes. In some of our data (*case 5*, fig. 2) the findings suggest that the basal metabolic rate increase precedes the rise in blood count, and in *case 6* (fig. 3) there is a fall in metabolic rate which precedes that of blood count. More extensive frequent observations are needed before conclusions are warranted on this point.

The rise in basal metabolic rate caused by androgens has been shown to be intimately connected with other metabolic shifts. Among them is a retention of protein (12, 15, 16). Under proper circumstances androgens also stimulate growth of new tissue, not only of the genitalia but also of skeletal muscle as well (17, 18). It appears likely that such a set of factors favoring growth may also facilitate the formation of blood cells.

The existence of anemia is not necessary for the demonstration of this effect, nor does the presence of a normal blood count in itself necessarily preclude the production of such a change. *Case 5* (fig. 2) and *case 7* had normal counts before therapy was begun and yet showed a striking response.

In the eight cases of hypogonadism reported here which had no obvious evidence of pituitary disease, the blood count was raised by methyl testosterone or testosterone propionate in seven. It may be of importance that the rise in blood count in the two patients in whom pituitary disease was present was relatively slight or insignificant. This suggests the possibility that pituitary hypofunction in some way

forms a barrier to as full a metabolic response to androgens as may otherwise occur.

The fact that body weight increases at the same time as the erythrocyte count does so, as well as the fact that there is no accompanying shift in leukocyte count, both attest to the fact that there is an actual increase in the number of red cells in circulation and that the findings are not the result of hemoconcentration. Whatever the actual mechanism of such a shift in blood count may be, these data suggest that the rise in blood count and possibly that of the metabolic rate as well may be a reproduction of changes observed in normal individuals during adolescence.

Such findings support the view that sex differences in blood count are hormonal and metabolic, not genetic in nature. In this sense the higher red cell count of the male may be considered a secondary sexual characteristic. It appears probable that excessive quantities of adrenal cortical steroids produce the increased erythrocyte counts seen in cases of Cushing's syndrome, adrenogenital syndrome and adrenal cortical tumor by a similar mechanism

The striking effect of androgens in raising the blood counts in cases of hypogonadism is apparent. The blood counts have increased from anemia levels to high normal in some instances. Such distinct changes as these bring to mind the possibility that androgens may be useful in the treatment of certain cases of anemia in which hypogonadism is not as apparent as in these cases.

SUMMARY AND CONCLUSIONS

Twelve individuals were treated with testosterone propionate, methyl testosterone, or both. Eight were eunuchoids without evidence of pituitary disease; two had hypogonadism with evidence of pituitary disorder; and two were sexually mature men.

Observations on the erythrocyte, hemoglobin, hematocrit and leukocyte levels of the circulatory blood were made over periods varying from 1 month to 8 years. Active treatment extended over more than 4 years in some cases.

In 7 of the 8 eunuchoid patients without pituitary disease, there was a rise in erythrocyte, hemoglobin and hematocrit levels with therapy or a fall on withdrawal of therapy, or both. In the others, the response was insignificant or absent.

Those patients showing a rise in blood count also showed a rise in B.M.R. which approximately paralleled it. An increase in metabolic rate occurred with treatment in the other cases, but on the whole it was less marked, and with a single exception (*case 10*) did not rise significantly above normal range.

These findings suggest that the changes in erythrocyte and hemoglobin levels observed with androgen therapy are related to changes in the basal metabolism and perhaps other intimately connected metabolic shifts. We believe we have reproduced a rapid form of change in the hematopoietic system which occurs more slowly in normal individuals during adolescence.

Attention is directed to the possible value of androgens in the treatment of certain cases of anemia.

We are grateful to Miss Irene Smith for valuable technical assistance.

REFERENCES

1. McCullagh, E. P., and R. Jones: Note on the effect of certain androgens upon the red blood cell count and upon the glucose tolerance. *Cleveland Clin. Quart.* 8: 79. 1941.
2. Boothby, W. M., and Irene Sandiford: Normal values of basal or standard metabolism. A modification of the DuBois standards. *Am. J. Physiol.* 90: 290, 1929.
3. Kenyon, A. T.: Personal communication.
4. Thompson, W. O., and N. J. Heckel: Male sex hormone; clinical application. *J. Am. Med. Assoc.* 113: 2124. 1939.
5. McCullagh, E. P., ahd H. R. Rossmiller: Methyl testosterone. II. Calorigenic activity. *J. Clinical Endocrinology* 1: 503. 1941.
6. Jones, R., E. P. McCullagh, D. R. McCullagh and G. W. Buckaloo: Methyl testosterone. IV. Observations on the hypermetabolism induced by methyl testosterone. *J. Clinical Endocrinology* 1: 656. 1941.
7. Riddle, O.: New data on the relation of metabolism to sex. *Proc. Second Internat. Cong. Sex Research 1930.* P. 180. 1931.
8. Blacker, N. J.: On the influence of sexual hormones upon the number of erythrocytes and percentage quantity of hemoglobin in fowl. *Biol. generalis* 2: 345. 1926.
9. Williamson, C. S : Influence of age and sex on hemoglobin. *Arch. Int. Med.* 18: 505. 1916.
10. Osgood, E. E., and R. L. Baker: Erythrocyte, hemoglobin, cell volume and color, volume and saturation index standards for normal children of school age. *Am. J. Dis. Child.* 50: 343. 1935.
11. Nathanson, I. T., L. E. Towne and J. C. Aub: Normal excretion of sex hormones in childhood. *Endocrinology* 28: 851. 1941.
12. Kenyon, A. T., K. Knowlton, I. Sandiford, F. C. Koch and G. Lotwin: Comparative study of the metabolic effects of testosterone propionate in normal men and women in eunuchoidism. *Endocrinology* 26: 26. 1940.
13. DuBois, E. F.: Basal Metabolism in Health and Disease. 3d edition. Lea and Febiger, Philadelphia, 1936.
14. Boothby, W. M., J. Berkson and H. L. Dunn: Studies of energy of metabolism of normal individuals: a standard for basal metabolism with a monogram for clinical application. *Am. J. Physiol.* 116: 468. 1936.
15. Kenyon, A. T., I. Sandiford, A. H. Bryan, K. Knowlton and F. C. Koch: Effect of testosterone propionate on nitrogen electrolyte, water and energy metabolism in eunuchoidism. *Endocrinology* 23: 135. 1938.
16. McCullagh, E. P., and F. J. McGurl: Effects of testosterone propionate on epiphyseal closure, sodium and chloride balance and on sperm counts. *Endocrinology* 26: 377. 1940.
17. Webster, B., and W. Hoskins: Influence of androgen therapy on growth rate of hypogonadal adolescent boys. *Proc. Soc. Exper. Biol. & Med.* 45: 72. 1940.
18. McCullagh, E. P.: Use of testosterone propionate in male hypogonadism. *Proc. Inerst. Postgrad. M. A. North America.* 1941. P. 93.

Gonadotropic Hormone: Modification of the Alcohol-Precipitation Assay Method

[Gonadotropin Assay]

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WITH THE ACCUMULATION of experience in the concentration and purification of the gonadotropic hormones isolated from the urine of normal (1, 2, 3) and endocrinological patients, a gradual evolution of the technical procedure (4) has taken place. The evolution has proceeded in the direction of reducing toxicity of the concentrate and increasing the simplicity and ease of preparing the concentrate.

The urine collections are made during a 12-hour overnight period, usually from 7 P.M. to 7 A.M. The specimens are kept in a refrigerator, without added preservative, until precipitated. Male patients are requested to collect four successive separate specimens. All are precipitated but only one specimen is assayed. If the assay results are high or normal, the remaining specimens are then completely concentrated and assayed separately to confirm the findings of the first. If the assay results are low, the remaining three specimens are pooled and the combined concentrate assayed in a single animal. Female patients are instructed to begin collections five days prior to their next anticipated menses. Often this necessitates collecting more than five specimens because of miscalculation. Only the last five are used. These are combined and a one-day aliquot is concentrated and assayed. If the assay results are low, a similar 2 or 3-day aliquot may be assayed. Otherwise the first assay is checked by further similar assays.

The five-day period preceding the next menses is chosen because of the greater likelihood of avoiding the main peaks of excretion of the menstrual cycle (3). Any peak which might occur during this period is minimized by the pooling process and thus a fair estimate of average function is attained.

All cloudy urine is filtered through soft filter paper to remove precipitated salts, mucin, and other debris. The entire 12-hour-urine specimen is then precipitated with 4 to 6 volumes of 95 per cent ethyl alcohol and permitted to settle overnight or longer. One gallon, wide-mouth, glass jars are suitable for precipitation. The alcohol-precipitated urine may stand in a refrigerator or cold room for months without appreciable loss of potency. The clear supernatant fluid is siphoned off and the residual precipitate is centrifuged 4 to 5 minutes in a 250 cc. centrifuge tube. The precipitate is washed twice with ethyl ether, centrifuging off the ether each time. Both the original wide-mouth container and tube are dried before a fan and the dried precipitate is transferred into an osmosis cellophane dialyzing bag.[1] Repeated tap water rinsings are made of both containers until all the precipitate has been transferred to the dialyzing bag. As much as 100 to 150 cc. of water may be used to effect the transfer. Smaller amounts of water offer no advantage since the volume often rises to this level during dialysis. The contents are dialyzed against cold running tap water overnight.

This procedure accomplishes original concentration of the protein hormone, elimination of the alcohol, fat-soluble substances, and especially steroids. The dialysis eliminates electrolytes and other molecules of low molecular weight. This step is highly important when large amounts of urine are being concentrated for injection into a single animal because the toxic substances (mostly salts) are dialyzed out. This is apparent in the lower fatality rate, and rarity of constitutional symptoms and local reactions, such as the matted skin and subcutaneous tissue about the injection site. Despite the foregoing precautions an occasional animal will die. The elimination of electrolytes during the 12-hour dialysis process has another advantage in that the protein hormones become more completely soluble as the amount of salt decreases.

After dialysis, the entire contents of the bag are returned to the original unwashed 250 cc. centrifuge

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[1] C.E.N.C.O. No. 70160A. Tubing 1 1/8 inches in width and 0.00072 inches thick.

tube and after the rinsings are added, the precipitate is centrifuged down. The supernatant liquid is poured off into beakers and reprecipitated with 4 to 6 volumes of 95 per cent ethyl alcohol, and the precipitate is permitted to settle overnight. Difficulty is occasionally encountered in causing the protein hormones to reprecipitate. A number of measures may be taken to obviate this difficulty, including vigorous stirring or shaking, increasing the concentration of alcohol, adding 0.5 mg. of NaCl, and adding 5 to 10 cc. of ethyl ether.

The clear supernatant liquid is siphoned off and the residue transferred to pointed-tip 50 cc. centrifuge tubes and centrifuged for 2 to 3 minutes. The precipitate is thoroughly mixed with ethyl ether and centrifuged again before it is dried in front of a fan, along with the precipitating beaker. This last step is virtually the same as the earlier washing and centrifuging of the first precipitation since here again the beaker is retained to be washed. It can also be used to hold the washings of the syringe.

The small dried cake of precipitate is most conveniently broken up with an 18-gauge, 2-inch needle attached to a 5 cc. syringe. Neutral distilled or tap water is flushed through the precipitating beaker with the syringe three separate times and added to the precipitate in the centrifuge tube three separate times, centrifuging off the final solution for use each time. The water is added in 3, 1½, and 1½ cc. amounts to both the beaker and centrifuge tube. The precipitate is completely broken up and exposed to the water by repeatedly drawing it up into the syringe and forcefully expelling it. The solution of hormone, now in the form for injection, is contained in a total volume of 6 cc. so that 1 cc. injections can be made twice daily for three successive days. If cloudiness or precipitates remain in the final injection solution, a further centrifuging of the whole amount before injection may eliminate this. Assay rats are 22 to 24 days old at the time of the first injection and are killed by rapid decapitation 14 to 16 hours after the final injection. Vaginal opening, although somewhat capricious for use as an assay end-point, is noted at autopsy. The uterus and ovaries are dissected free and weighed separately (preferably on a Roller-Smith torsion balance) as previously described (5).

Results, using the above simplified procedure, have been more uniform, and slightly higher than with the use of previously described methods.

REFERENCES

1. Heller, C. G., and E. J. Heller: *J. Clin. Investigation* 18: 171. 1939.
2. Heller, E. J., C. G. Heller and E. L. Sevringhaus: *Endocrinology* 29: 1. 1941.
3. Heller, E. J.: *J. Clinical Endocrinology* 1: 813. 1941.
4. Heller, C. G., and E. J. Heller: *Endocrinology* 24: 319. 1939.
5. Heller, C. G., H. D. Lauson and E. L. Sevringhaus: *Am. J. Physiol.* 121: 364. 1938.

ADDENDA

R. F. Varney and F. C. Koch, reporting in *Endocrinology* 30: 399, March, 1942, suggest that dialysis causes marked reduction in gonadotropic potency. This contention is not completely borne out by detailed examination of their data, especially Tables 6, 7 and 8. If the reduction in potency following dialysis, as obtained by them, is more real than apparent a possible explanation could be variations in the cellophane osmosis membranes used. One notes that deaths occurred in many of their assay animals regardless of the extraction method used. The extracts prepared by the alcohol-dialysis-alcohol precipitation method have, in our experience, caused death in less than one per cent of the animals.

The Effect of Pregnant Mare Serum Hormone on a Case of Primary Hypo-ovarianism

[Ovary and Gonadotropin]

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THE FOLLOWING CASE of primary hypo-ovarianism is presented because of its typical signs and symptoms and to demonstrate the production by treatment of the physiological phenomena of a normally approaching puberty.

CASE REPORT

G.P., age 15 years and 9 months, was first seen at the Greenpoint Hospital Out-Patient Clinic on April 6, 1940.

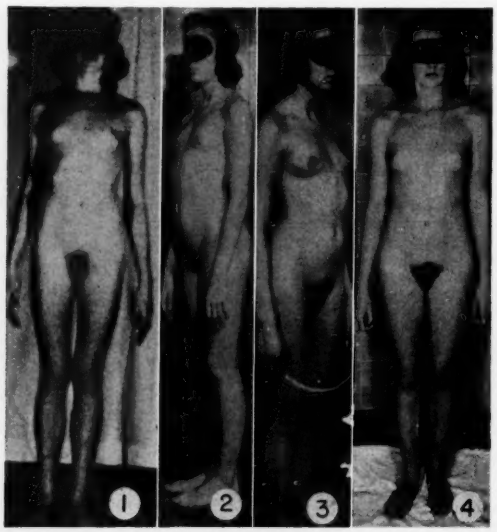

Fig. 1. G.P., age, 15 years and 9 months; before treatment, 4/6/40. Fig. 2. After treatment was discontinued 10/24/40. Fig. 3. Three months later, 2/28/41. Fig. 4. One year later, 2/18/42.

The fact that she had grown 5 inches in height during the preceding year was the chief complaint made by her mother. Besides not having menstruated as yet, headaches, frequent colds, and constipation associated with cramps, completed the story of accompanying symptoms.

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She was a full-term baby, weighing 10 pounds at birth, and she developed normally. Pubic hair and a slight bulge about the mammilla had appeared at fourteen and one-half years. These have not increased in amount or size during the last year. Headaches over the right side of the head occur frequently. She is agreeable and helpful at home but shows no sign of sociability; nor does she take any interest in outside activities. Her school work is just passable.

The maternal grandmother and paternal grandfather were obese; her father is tall and stout; her mother tends towards obesity and is of a neurotic disposition; one brother, older, is apparently normal.

Examination. G.P. is a tall, thin and pale girl. One is struck at once by her eunuchoid proportions, her juvenile visage, and her quiet and reserved demeanor. Although she co-operates perfectly and is agreeable to all routine requirements, a definite shut-in personality with an absence of normal aggressiveness is evident.

The skin is pale with no blemishes. There is no axillary hair; the pubic hair is scant; the escutcheon, normal. Decreased somatic development is apparent in her long, thin frame (figure 1). The small mammary bulge is soft and insensitive. The abdomen is thin and flat. Teeth are rather well-spaced; dentition moderate. The heart and lungs are normal. The external genitalia appear hypoplastic and dry; no internal examination was made.

The body weight is 108 pounds; the height, 64½ inches; span, 68 inches; lower measurement, 34 inches.

The B.M.R. is normal; the blood count relatively normal; hemoglobin, 75 per cent. The roentgenogram revealed the olecranon epiphysis to be partially united; the metacarpal and phalangeal epiphyses show no sign of union. The bone age is about 13 years (1, 2).

The vaginal smears are dry, the material is scant and obtained with difficulty. When stained with crystal violet the smears reveal thick clumps of material containing a few well-defined cells, many of which are from the deep layers, and very little debris. The picture microscopically is one of well-advanced atrophy of the vaginal epithelium (fig. 5).

Summary of findings. There is an absence of the menarche; a delay and absence of progressing development of secondary sexual characteristics; an overgrowth of the long bones producing eunuchoid proportions; a delayed union of the epiphyses; poor somatic development; juve-

nile mannerisms and psyche; an absence of signs and symptoms pointing to the thyroid or pituitary glands as possible causes for the ovarian deficiency. These signs, varying in degree only, are cardinal and comprise the diagnosis and differential diagnosis of primary hypo-ovarianism (1, 2).

Treatment. Treatment was begun on May 6, 1940. Intramuscular injections of pregnant-mare-serum hormone, 400 international units[1] were given daily for 12 days beginning every 28th day. Thyroid extract, 1 grain daily was prescribed. Vaginal smears were taken every other day.

Results of therapy. Towards the end of June, after the second course of treatment, the mammary glands showed signs of resuming growth. At the same time the vaginal smears became more moist; the clumps of cells less compact; the individual cells more discrete, and changed from oval to a pentangular form; deep cells were numerous. During the next month evidence of proliferation of the vaginal mucosa could be found in the appearance of large, well-defined cells, a diminution of the number of deep cells, and a normal amount of bacteria and leucocytes. From that point on, improvement in the appearance of the vaginal smears took place in a sequence not unlike that seen in the smears of menopausal women receiving estrogenic therapy (3). On Aug. 30, 1940, the smear contained uniformly large cells and a few leucocytes. Two days later the smear contained typical cornified cells only. Within 24 hours bacteria and leucocytes appeared in large numbers, the cells became elongated and the nuclei were large. Within the last week prior to menarche the character of the smears changed rapidly and they resembled closely those observed in the premenstruum of normal women. In a broad sense a comparison of the vaginal smears in this case may be made with those of prepubertal girls as they approach normal puberty (4). In the latter instances, however, the process is slower and demonstrable only over a longer period of time.

Although at no time during treatment with gonadotropin was estrogen given, the vaginal smears became clearer and cleaner as bacteria and leucocytes gradually diminished in amount until on Aug. 30, 1940 (fig. 8), after the fifth course of treatment, there appeared a vaginal smear containing typical cornified cells (5). The menarche occurred on Sept. 10, 1940, lasted 7 days and was accompanied by no discomfort. All treatment was discontinued at this time (fig. 2).

By Feb. 28, 1941, no further excessive linear growth had occurred and the olecranon epiphyses were completely united; the epiphyses of the hand were partially united; the menses had recurred normally and regularly to date; the secondary sexual characteristics continue to show improvement (fig. 3.)

On Feb. 18, 1942 the growth recorded since treatment was started is ½ inch; the hand epiphyses are completely united; the menses appear normal and regularly. In every way the patient has developed into an apparently normal young woman. The eunuchoid proportions naturaly remain (fig. 4).

DISCUSSION

We have been dealing with a condition, all symptoms of which can be attributed to the absence of estrogenic hormones (6, 7, 8). The processes of maturation resulting in puberty are synchronized culminations of physical and physiological interrelationships (6–11). In order for the ovary to play its part properly in these reactions, it must produce estrogen, not only for its effect on the genital and somatic systems, but also for its effect on the other ductless glands (6, 8). To accomplish this effectively its development must be completed according to a physiological schedule.

It is believed at present that the ovary at birth is composed of a large cortex which contains primordial follicles. Deep in the medulla, primary follicles containing the definitive germ cells attempt to develop but, their span of existence being short, they soon undergo atresia or cyst formation (11, 12). In the next 12 to 14 years, the entire cortex disappears, while the follicles in the medulla survive for longerperiods and gradually succeed in producing some estrogen before being inactivated (6). The cumulative result of this prepubertal follicular activity produces the estrogen responsible for the secondary sexual characteristics and prepares the genital tract for puberty. Finally, when the entire original cortex has disappeared, the large follicles near the surface of the ovary can rupture and liberate their ova. Thus, in the ovary itself, there are morphological changes which must also be completed according to schedule since, no matter how large the follicle, or how great the amount of estrogenic hormone produced, unless the infantile cortex disappears, rupture of the follicle through the surface of the ovary to release the ovum is impossible. A delay in rupture necessarily results in death of the ovum, little or no luteinization, and above all, little chance for normal rhythmic ovarian physiology (6, 7, 11, 12).

In primary hypo-ovarianism, in which no other glands seem to be responsible for the gonadal insufficiency, it has been assumed that the gonads themselves are refractive to gonadotropic stimulation (1, 2). But this apparent refractiveness may well be an inability to respond on the part of an ovary whose development is so much retarded as to make it appear that all function has ceased. Immature ovaries cannot be expected to react to gonadotropic influences as do mature ones, i.e., with follicle rupture, ovulation, and luteinization (6, 7). Refractiveness, therefore, may be an incorrect term. The ovary in question may be actively undergoing histological changes, and may even make up for its retardation under active spurring by an exogenous gonadotropin. Conditions produced by a prenatal unbalance of maternal hormones (12,

[1] The gonadotropic hormone from the serum of pregnant mares (Anteron) was supplied by the Schering Corp., Bloomfield, N. J.

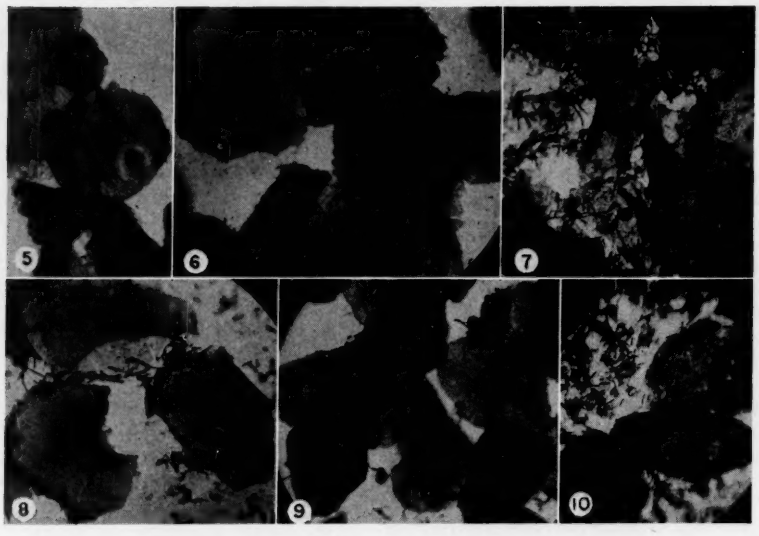

Fig. 5. Vaginal smear made before treatment begun. Fig. 6. Type of smear during first 3 months of treatment. Fig. 7. Smear made early in August, 1940. Nuclei tend to be smaller, cells more regular.

Fig. 8. Aug. 29, 1940; uniform cells, small picnotic nuclei; smear is clearing up. Fig. 9. Sept. 1, 1940 illustrating maximum estrogenic effect. The cells are clear, debris and leucocytes absent. Fig. 10. Three days later; premenstrual smear.

13), developmental anomalies, intercurrent diseases and nutritional disturbances (14) may well cause delays and arrests in the maturing processes of the ovary without producing actual deleterious effects.

It would appear that the ovaries of this patient completed their development under re-inforced gonadotropic stimulation and continued to function normally.

SUMMARY

A case of delayed puberty in a fifteen-year and nine-months-old female in whom all signs pointed to an arrested ovarian development, was treated with the gonadotropic hormone from pregnant mare serum. The resumption of ovarian development was evidenced by: *a*), Mammary development and the increase of pubic hair; *b*), curbing of excessive linear growth; *c*), closure of the metacarpal and phalangeal epiphyses; *d*), alteration of the character of the vaginal smears; *e*), the continuation of normal and regular menses. The gradual improvement in the general condition, and the absence of any signs of regression of the recently developed characteristics in 16 months following cessation of treatment, substantiate the completed puberty of our patient.

CONCLUSION

In the treatment of primary hypo-ovarianism it is necessary to correlate the presenting signs and symptoms with the manifestations of ovarian activity as expected from its state of development. In the evaluation of the effectiveness of a gonadotropic hormone, alterations in the secondary sexual characteristics and the vaginal smears are the only criteria.

REFERENCES

1. Engelbach, W.: Endocrine Medicine. Charles C Thomas, Springfield, Illinois, 1932.
2. Hamblen, E. C.: Endocrine Gynecology. Charles C Thomas, Springfield, Illinois, 1939.
3. Papanicolaou, G. N., and E. Shorr: *Am. J. Obst. & Gynec.* 31: 806. 1936.
4. Fraenkel, L., and G. N. Papanicolaou: *Am. J. Anat.* 62: 427. 1938.
5. Papanicolaou, G. N.: *Am. J. Anat.* 52: 519. 1933.
6. Novak, E.: *Am. J. Obst. & Gynec.* 37: 605. 1939.
7. Engle, E. T.: *A. Research Nerv. & Ment. Dis., Proc.* 17: 298. 1938.
8. Moore, C. B., G. F. Simmons and L. J. Wells: *Anat. Rec.* 63: 279. 1934.
9. Smith, P. E., and E. T. Engle: *Am. J. Anat.* 40: 159. 1927.
10. Smith, P. E.: *Proc. Soc. Exper. Biol. & Med.* 24: 131. 1926; 24: 337. 1926.
11. Simkins, C. S.: *Am. J. Anat.* 51: 465. 1932.
12. Neuman, H. O.: *Ztsch. f. Geburtsh. u. Gynäk.* 99: 100. 1930. Abderhalden Handbuch der Arbeitsmethoden Abt. VIII: T.1/11.
13. Engle, E. T.: *Endocrinology* 16: 513. 1932.
14. McCollum, E. V.: The Newer Knowledge of Nutrition, Macmillan Co., New York. 1922.

Intersexuality Associated with Malignant Intra-Abdominal Teratoma of the Seminoma Type

[Intersexuality]

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CASES OF INTERSEXUALITY associated with a malignant intraabdominal teratoma of the testis are rare and the case herein reported had interesting features which make it worth recording.

REPORT OF CASE

History. A girl, aged 14, American, was referred on July 14, 1941 by the Board of Education because of 'gland trouble.' Psychiatric tests showed that her intelligence quotient was normal. She had been reared as a girl, played with dol's and had led a normal female child's existence.

The father stated that three years ago, at the age of 11, her voice became masculine in character, assuming a deep pitch. The mother gave the information that her genitals 'did not seem right.' She had never menstruated and there had been no epistaxis.

Her past history had been uneventful, having had measles, chickenpox and mumps. The tonsils had been removed because of chronic tonsillitis.

The parents are of average height and weight. Their intelligence is normal. A brother was reported as being normal.

The patient was well-nourished and in the nude gave the impression of a male. The hair was black and the voice was deep pitched and of a masculine character. The measurements were as follows.

	Patient		Normal	
	Inches	Centimeters	Inches	Centimeters
Circumference of head	22.25	56.5	21.5	54.6
Chest	32.25	82	29.3	74
Waist	27	68.5	24.7	62.8
Span	67.5	171	62.4	158.7
Upper	32.5	82.5	30.9	78.7
Lower	30.5	77.5	31.1	78.7
Height	63	83.8	62	81
Weight	116 lb.	52.6 kg.	104.5 lb.	47.5 kg.

There was hirsutism of the upper lip and the hair in the temporal regions extended onto the cheek below the tragus of the ear. A high arched palate was present. The thyroid gland was palpable. The breasts were flat and of the male type. A presystolic murmur was heard at the apex of the heart. The pelvis was of the android type. There was a feminine type of pubic hair distribution and it was thick and long. Protruding from the pubic hair was a rudimentary penis (fig. 1).

There was a marked development of hair on the labia majora extending to and around the anus. The penis in a flaccid condition measured 5 cm. (fig. 2). The glans penis on the upper portion was surrounded by normal appearing prepuce, which could be moved forward so as to completely cover the glans. On the under surface of the penis was a raphe corresponding to the penial urethra and each half of the raphe extended laterally merging with and making up the labia minora (fig. 3). As we know, the urethral folds, which persist in the female and fail to fuse as they do in the male, form the labia minora. In the vestibule of the vagina was a normally placed female urethra.

A vagina with a hymen admitting one finger was present. The roentgenologist's interpretation of the vaginogram which was made was as follows.

"Twenty cc. of lipiodol was introduced into the vagina. There is a definite vaginal vault which is slightly inclined towards the right. We would consider the vault to be of average size for a patient of this age, although it is somewhat shallow and at the distal end tapers off into a rather small lumen suggestive of a shallow canal. The films show that the pelvis is small and of the android type and rather narrow." Dr. E. Witwer.

On rectal examination no uterus could be palpated. No testicles could be felt in the inguinal region.

The legs were muscular and masculine, the lower extremities were covered with black hair adding to their masculine appearance.

The hands were soft and feminine in type, and the nails were covered with nail polish.

Laboratory examination of the blood gave normal values for blood sugar, nitrogen, calcium, phosphorus and cholesterol. The blood phosphatase was 5.5 Bodansky units, which is normal for her age.

The blood count was normal except for a preponderance of lymphocytes (52%) in the differential count. The Kahn blood test was negative. The urine examination was repeatedly negative. The systolic blood pressure was 132, the diastolic 58 mm. Hg.

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The basal metabolism was minus 8 per cent.

The parents, being disturbed by the genital abnormality of the patient and convinced that she was a female in habits and actions, requested that the penis be removed. This was agreed to and it was further proposed

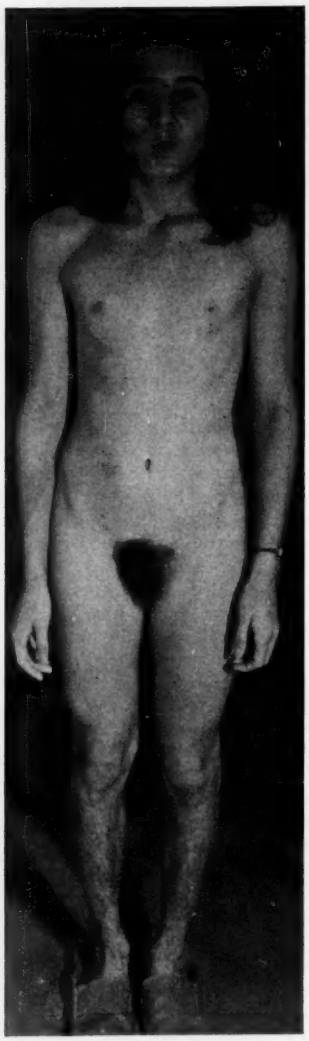

Fig 1. Configuration of body with male type breast, rudimentary penis.

to do an exploratory laparotomy. Consequently on July 23, Dr. N. Allen performed a 6-inch low median laparotomy. Both adrenal areas were palpated, the surgeon's impression being that there was no abnormal enlargement. The spleen was freely movable. The right lobe of the liver was enlarged.

Examination of the pelvis revealed that a rudimentary uterus (finger-like in shape) approximately 4 cm. long and 2 cm. in diameter was present. It was embedded in tissue resembling the broad ligament. Extending from the uterus were the right and left fallopian tubes with their fimbriated ends. On the right side just beneath the fallopian tube, near its distal end and normally situated was a small but normal-appearing ovary. About 2 inches (5 cm.) from the rudimentary uterus was a testicle, 2 cm. long, bluish-white in color. It was easily removed.

On the left side, in the same relative position as on the right beneath the fallopian tube was a testicle about 2 cm. in diameter, white in color with a shiny capsule. This was removed. There was a definite contrast between the bluish-white color of the right testicle and the white fibrous appearing testicle on the left side. Neither tube nor rudimentary uterus was removed, and the right ovary was also not disturbed. Appendectomy was performed.

Following closure of the laporatomy wound, the patient was put up in stirrups and a catheter inserted into the bladder. The entire penis was removed and a plastic reconstruction was done (fig. 4).

Other than a superficial infection of the abdominal wound which caused a fever for 10 days, her recovery was uneventful.

The pathological report was as follows.

"The penis with a normally formed glans and prepuce, measures 5 cm. No evidence of an orifice. On section two oval shaped brown areas of tissue—corpora cavernosa penis.

There are two rounded slightly flat masses, the right one is 2 cm. long. bluish-white in color and on section show a yellowish-white papilliferous mass apparently not divided by fibrous septae, doughy in consistency. The left mass, pearly white in color, is firm and there is a white mass encapsulated from the surrounding parenchyma."

The microscopic report was. "1. Cavernous tissue.

2. Right testis: malignant teratoma of the seminoma type (fig. 5). The stroma is richly infiltrated with lymphocytes and is composed of large round cells of the embryonal type. There is every indication of a rapid growth of the malignant embryonal element.

Left testis: Epidermoid cyst in hypoplastic testis."

On July 18, a 12-hour specimen of urine totalled 1615 cc. Gonadotropic hormone assay was made according to the method of Heller and Heller (1). Injection into a rat produced a 1+ vaginal opening. The uterine weight was 90 mg. and the ovarian weight was 87.5 mg. The amount of the hormone present was the same as that usually found in castrate or menopausal urine.

On Jan. 10, 1942, approximately 6 months after operation, a 12-hour specimen of urine totalled 2225 cc. The same procedure for gonadotropic hormone assay in the rat produced a negative vaginal opening. The uterine weight in the rat was 21.1 mg. and the ovarian weight was 14.4 mg. This type of assay response would be normal for a 14-year-old girl who had not reached puberty. There is sufficient contrast between the gonadotropic content of the urine in the pre-operative and post-operative periods to be of some significance. However, deductions from single assays cannot be made with any conclusiveness.

COMMENT

The parents of the child stated that they had not seen anything abnormal about her genitals when she was a baby. Her father had frequently bathed her and did not see any abnormality. The parents and the patient agreed that the voice became masculine three years ago at the age of eleven.

As a child she played with dolls and acted like a normal female. At the age of 11 she took up sewing and applied nail polish. She attended school at the age of 6, did well in her classes, and at present is in the 9th grade. She never had epistaxis or a bloody vaginal discharge. The hirsutism of the upper lip and legs, the enlargement of the penis, and the masculine

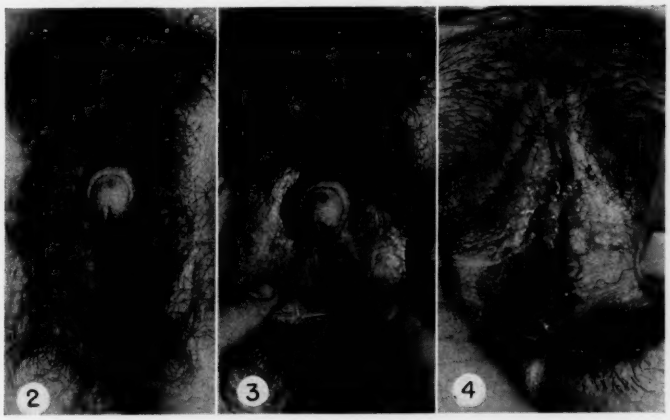

Fig. 2. Rudimentary penis. Fig. 3. Penis with raphe, lateral walls of urethral folds forming labia minora. Normal appearing vaginal opening. Fig. 4. Vulva after removal of penis and plastic reconstruction.

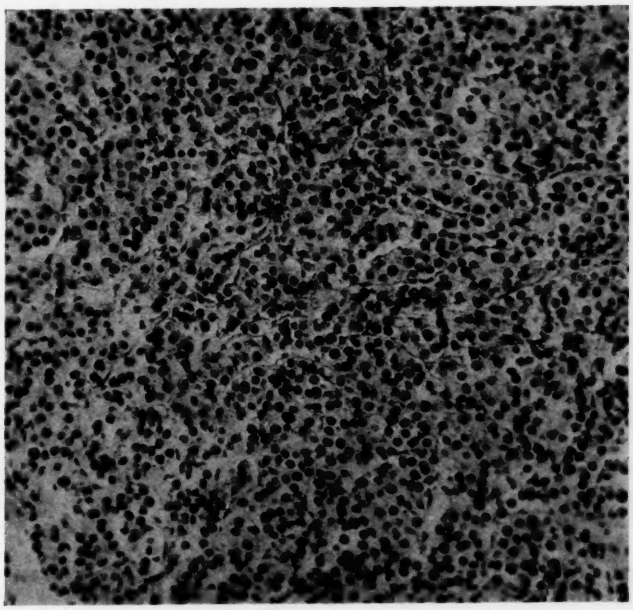

Fig. 5. Teratoma of the testicle of the seminoma type.

voice all appeared at about the same time, 3 years ago.

One might assume that the intra-abdominal testis and specifically the active right testis gave off testicular hormone at this time when the patient was nearing puberty. As to when the tumor became actively malignant is of course uncertain.

Young (2), in his treatise on genital abnormalities and hermaphroditism said, "The gonadal anlage may be reversed and hormonal factors also may contribute to the sexual deflection by secretory hormones which have opposite effects than those normally secreted by the developing ovary or testis, as the case may be. What started out to be anatomically an ovary might secrete androgenic substances similar to chemical structures and biological actions to the testis hormones. Hormonal intersexuality is probably a phenomena of later embryonal life just as it sometimes occurs in adults with masculinizing tumors. It is probable, according to Goldschmidt's hypothesis, that most pseudohermaprodites are on a genetic basis and the chromosomal structure of all their body cells are either the male or female formula. However, the opposite sex determining factors or forces in the individual cells are dominant and much greater, so at some point (drehpunkt) in development they turn the future development into a cell having the opposite sex characteristics." The latter is probably what took place in the patient here reported.

The approach of puberty set the sex mechanism in motion and the dormant testis teratoma became activated so that hermaphroditism then followed. The right testis in contrast to the left testis as the pathological report shows, was no doubt the responsible factor for the hermaphroditism.

Vastola (3) reported in interesting male hermaphrodite, aged 37, with a pelvic tumor. This was revealed on laporatomy to be an embryonal carcinoma of an abdominal testis with a twisted pedicle and hemorrhage into the tumor mass. Dr. James Ewing who examined the specimen stated that it was a large round and polyhedral-cell carcinoma. It was atypical teratoid cancer and of teratoma origin not derived from the tubule cells, as tumors that may possibly originate from tubule cells and may be called seminoma generally are more alveolar in structure and lack lymphoid stroma. Yet Ewing did not insist too strongly on the exact derivation of this particular tumor which impressed him as an embryonal growth.

Carmichael and Oldfield (4) reported a case of male pseudohermaphroditism in a 'girl,' aged 14, with a large intra-abdominal teratoma. The tumor, which arose by a short pedicle from the site of the left ovary, was removed along with the fallopian tube and broad ligament. Its removal revealed an abnormality at the site of the right ovary, there was no ovary proper but only a small nodule of what appeared to be ovarian tissue in the posterior layer of the broad ligament. The uterus and right tube were small but otherwise normal. The tumor was found to be a 'typical small-cystic teratoma containing numerous derivations of all three germ-layers, some at a primitive embryonic stage of development, others with a fully differentiated adult structure.'

Klaften (5) reported a case of pseudohermaphroditism associated with a large-celled ovarian carcinoma. He discussed the origin of these ovarian tumors which give rise to pseudohermaphroditism. They begin, he said, as a solid tumor of the ovary which was designated for a long time as alveolar sarcoma. Von Werdt called them solid granulosa cell tumors and derived from unused granulosa cell elements. Robert Meyer said that these tumors have all various types of designations. Von Pick termed them 'epithilioma chorioectodermale'; Von Krompecher gave them the name 'endothelioma'; Von Werdt 'granuolosa cell tumors'; Von Chevassu 'seminome'; Ewing, 'Embryonal carcinoma of the testicle'; Klaften favored R. Meyer's term 'disperminome.'

Ewing (6) in discussing the embryonal tumor of the testis said, "The most frequent tumor of the testis is composed of large round or polyhedral cells of embryonal type, lying diffusely or in large alveoli. The stroma is often richly infiltrated with lymphocytes. Through the demonstration by Wilms, Ohkubo and others, that many of these tumors contain teratoid elements, the suspicion first stated by Langhans, that the tumors are teratoid, has been confirmed. Yet Chevassu, Debornadi, and others derive this tumor from the spermatoblasts or embryonal equivalents, and separate this group from the teratomas with which they are so often associated. Several considerations forced the writer to conclude that this common tumor of the testis is always a one-sided development of a teratoma, and is not derived from the adult spermatoblasts." Ewing then goes on to give these reasons.

SUMMARY

A case of hermaphroditism in a girl aged fourteen is reported. A 5 cm. long penis-like structure with a normal appearing glans penis and prepuce was present. A normal-sized vagina, a rudimentary uterus, normal tubes with a right and left sided testis and a right-sided ovary were present. The testis on the right side was a highly malignant teratoma of the seminoma type. The left testis was hypoplastic and contained an epidermoid cyst. The body build was of masculine type as was the voice and hair distribution.

Her inclinations and habits were those of the female sex. Gonadotropic hormone assay before and after

operation reveal a significant difference in that preoperatively the amount corresponded to that found in the urine of castrate and menopausal women, whereas 6 months post-operatively the amount was normal for a 14-year old girl.

At the present time (February, 1942) she is doing well in school, engages in the usual activities with other girls, goes swimming without embarrassment, does sewing, uses lip rouge and nail polish. She considers herself a normal girl.

REFERENCES

1. Heller, C. G., and E. J. Heller: Gonadotropic hormone urine assays of normally cycling menopausal, castrates and estrin treated human females. *J. Clin. Investigation* 18: 171. 1939.
2. Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases. Williams and Wilkins Company, Baltimore, 1937.
3. Vastola, A. P.: Embryonal carcinoma of abdominal testis in pseudohermaphrodite. *J. Am. Med. Assoc.* 101: 111. 1933.
4. Carmichael, R. and C. Oldfield: A case of complete male pseudohermaphroditism with intra-abdominal teratoma testis. *J. Path. & Bact.* 39: 617. 1934.
5. Klaften, E.: Beitrag zur Kenntnis des soliden grosszelligen Ovarialkarzinoms bei Pseudohermaphroditismus. *Zentralbl f. Gynäk.* 56: 1989. 1932.
6. Ewing, J.: Neoplastic Diseases. W. B. Saunders Company, Philadelphia. 1928.

Effect of the Vitamin B Complex in Diabetes Mellitus[1]

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Because members of the vitamin B complex are concerned in carbohydrate metabolism, it has been suggested that they might have an ameliorating effect in diabetes mellitus. Clinical trials (1) with thiamine hydrochloride have been disappointing, but in experimental diabetes, Chaikoff and Kaplan (2) have shown that the administration of whole vitamin B complex prolongs the life of depancreatized dogs. We have, therefore, tried the vitamin B complex in clinical diabetes, but without benefiting the condition.

METHODS

Assessing the effect of a therapeutic measure in diabetes is difficult because of the great fluctuations in severity which many patients manifest. Elderly diabetics, in particular, often may take 20 to 30 units of insulin daily less than their true requirement, and only gradually over weeks develop marked glycosuria. The effect of infections is likewise well-known. It is possible that serial glucose tolerance tests would be the most accurate criterion for judging the condition of a diabetic, but such tests were not made in our patients. Patients in two principal categories were used. *a*). Those who took no insulin but had glycosuria, in whom improvement could be shown by a decrease in the amount of sugar lost in the urine. *b*). Those taking insulin, who could be rendered sugar-free, or could have their dose of insulin reduced.

Only patients were chosen whose long (months to years) attendance in the Diabetic Clinic had led to more or less constant values for body weight, insulin dosage (doses varied from 0 to 120 U daily) and degree of glycosuria (from none to 3 plus by Benedict's test). The patients were observed at weekly or biweekly intervals while taking the vitamin B preparation. During subsequent periods when the vitamin preparation was withdrawn a placebo resembling the vitamin preparation was given.

The vitamin B complex, a heavy syrup obtained from rice bran, was given in a dose of one ounce daily.[2] This amount contained the following quantities of vitamins: thiamine hydrochloride, 4.5 mg.; riboflavine, 300 micrograms; vitamin B_6, 4.5 mg.; nicotinic acid, 60 mg.; pantothenic acid, 12 mg.; the filtrate factor (Jukes-Lepkovsky) was 28 per cc.

RESULTS AND DISCUSSION

Twenty-one patients were given the vitamin B complex for periods of from 3 to 16 weeks, with the results shown in table 1. There was no significant change in weight, glycosuria or insulin requirement. The slight increases or decreases noted were only 1 or 2 pounds of body weight, a change of one plus in the Benedict's reaction, or a change in insulin dosage of 2, or at most 4 units.

Although both insulin and members of the vitamin B complex are involved in carbohydrate metabolism, and may to some extent be supplemental as demonstrated in animal experiments, this summation of action could not be shown in diabetic patients. Many of the patients felt better generally, especially, in that they slept better and their appetites improved. This is to be interpreted as a rectification of an unrecognized deficiency state rather than as amelioration of the diabetes.

CONCLUSIONS

Large doses of a potent vitamin B complex preparation, given for periods up to 16 weeks to diabetic patients, had no discernible effect on the severity of the disease.

REFERENCES

1. Smith, K. A., and H. L. Mason: Thiamin and diabetes mellitus. *Proc. Staff Meet., Mayo Clin.* 15: 529. 1940.
2. Chaikoff, I. L., and A. Kaplan: On the survival of the completely depancreatized dog. *J. Nutrition.* 14: 459. 1937.

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[2] The vitamin B complex (Galen "B"), and the placebo used were furnished by the Galen Laboratories of Berkeley, California.

TABLE 1. COMPARISON WITH PREVIOUS CONTROL PERIODS

Patient	Drug[1]	Duration of Medication, Weeks	Insulin Requirement	Glycosuria	Body Weight	Remarks
1	B	12	Same	Slight decrease	Same	Feels and sleeps better
	P	2	Same	Slight increase	Same	
2	B	12	Same	Same	Same	
	P	12	Same	Same	Same	
3	B	12	Same	Same	Same	Feels the same
	P	12	Same	Same	Same	
4	B	12	Same	Same	Same	Feels the same
	P	4	Same	Same	Same	Feels the same
	N	6	Same	Same	Same	Feels the same
5	B	5	Slight decrease	Same	Slight decrease	Feels better
	N	11	Same	Same	Same	Feels better
6	B	3	Increased	Increased	Same	Feels the same
	N	12	Increased	Same	Decreased	Feels the same
7	B	16	Same	Same	Same	Feels better; appetite
	P	6	Same	Same	Same	better
8	B	12	Slight increase	Same	Same	Feels same; appetite better
	N	2	Same	Same	Same	Appetite better
9	B	15	Same	Same	Same	
	P	4	Same	Same	Same	Feels worse
10	B	3	Same	Same	Same	
11	B	12	Same	Same	Same	
	P	8	Slight increase	Same	Same	
12	B	8	Same	Same	Same	
13	B	16	Same	Same	Same	
	B	8	Same	Same	Slight increase	
14	B	4	Same	Same	Same	
	P	4	Same	Slight increase	Same	
15	B	16	Same	Same	Slight increase	
16	B	8	Slight increase	Same	Same	Feels better
17	B	8	Same	Same	Same	
18	B	8	Same	Same	Same	
	P	4	Same	Same	Same	
19	B	4	Same	Same	Same	Feels the same
20	B	12	Increased	Same	Same	
	P	8	Increased	Same	Same	
21	B	4	Same	Slight increase	Slight decrease	
22	B	12	Same	Same	Same	
	P	8	Same	Same	Same	

[1] B, vitamin B complex; P, placebo; N, neither vitamin nor placebo.

Repeated Glucose Tolerance Tests in Hyperthyroidism

[Thyroid and Glucose Tolerance]

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THIS STUDY, based on 131 repeated glucose tolerance tests, performed before and after operation, in fifty cases of hyperthyroidism, constitutes one part of a comprehensive investigation on repeated glucose tolerance tests in children, in adults, and in adults with hyperthyroidism. The results in the first group have already been published (1). The results in the group of adults without hyperthyroidism are now in preparation.

The glucose tolerance tests in all instances were performed on fasting patients. One hundred grams of glucose was administered by mouth in 250 cc. of water, with a bit of citric acid added to the solution. Then samples of blood were withdrawn one-half hour, one hour, two, three and four hours after the ingestion of the glucose solution. The determinations of the blood sugar were made on one cc. of blood, with the Myers' modification of the Benedict method.

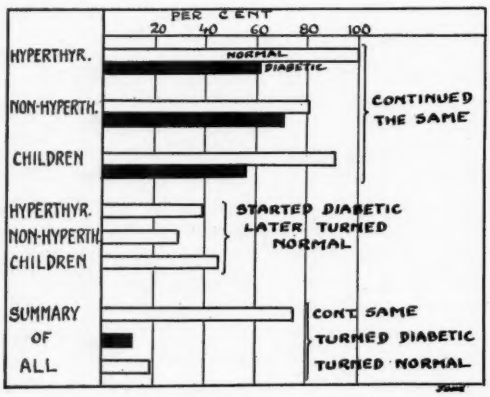

Fig. 1. COMPARISON OF THE RESULTS OF REPEATED GLUCOSE TOLERANCE TESTS IN THREE GROUPS OF PATIENTS: adults with hyperthyroidism, adults without hyperthyroidism, and children.

The object of this particular study was to note the effect of hyperthyroidism and of thyroidectomy on disturbed or normal carbohydrate metabolism, and to compare these findings with those obtained in the other groups of cases, that is, in children (patients less than 20 years of age), and in adults who did not have hyperthyroidism. These comparisons are shown graphically in figure 1. The most striking fact shown by this chart is that patients with hyperthyroidism who displayed a normal glucose tolerance curve at the outset continued to show a normal curve, indicating that the carbohydrate metabolism remained intact, in spite of hyperthyroidism. This 100 per cent incidence of a continued normal curve is much higher than in the adults who did not have hyperthyroidism, and also than in the group of children. Since the incidence of diabetes in patients with hyperthyroidism is greater than the general incidence of diabetes by more than 100 per cent the complete stability of the normal glucose tolerance curve in these patients with hyperthyroidism would suggest that when the carbohydrate metabolism remains normal despite the stress of hyperthyroidism, it must indicate that the individual patient has a good insulogenic reserve.

The stress of hyperthyroidism is temporary, and if it is due to factors other than an effect on the insulogenic apparatus itself, it might be expected that a considerable number of patients who displayed a disturbance of carbohydrate metabolism during the period when the thyroid was hyperactive would show a return to normal when this was eliminated by operation or other means. The data in figure 1 show that this was true in comparison to the group of adults who did not have hyperthyroidism. The percentage of patients with hyperthyroidism whose glucose tolerance curves returned to normal was 38.7 per cent, while in the patients who had no hyperthyroidism, the figure was 29.6 per cent. In the group of children, the percentage that returned to normal was higher than in the hyperthyroid group, 45.5 per cent. But this figure was based on only 19 cases, so the percentage figure may be misleading. If the values for the adults and children are grouped, the average for the two is 31 per cent, which indicates that the return to normal is considerably higher in the hyperthyroid group.

In the three groups of cases we find that in 80.6 per

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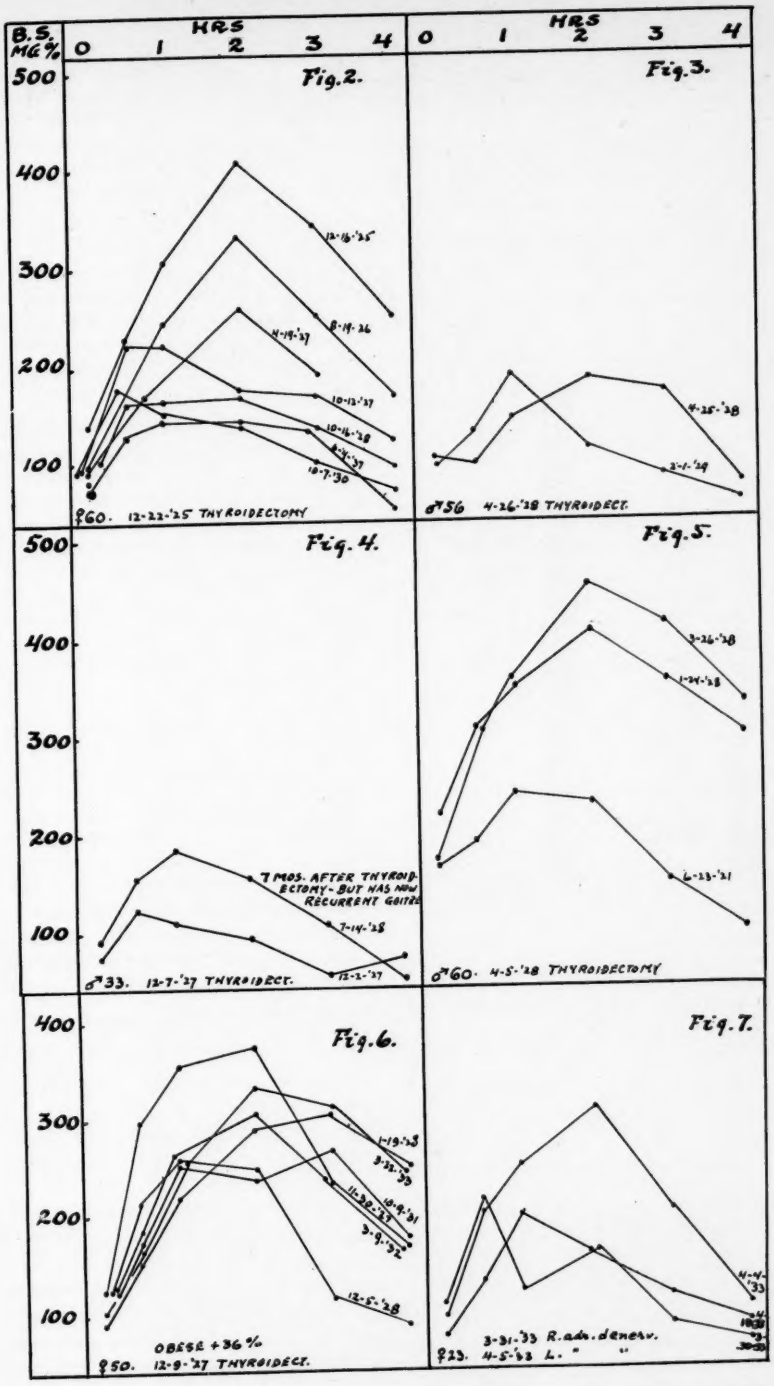

Fig. 2. Glucose tolerance tests in *case* 1. Fig. 3. Glucose tolerance tests in *case* 2. Fig. 4. Glucose tolerance tests in *case* 3. Fig. 5. Glucose tolerance tests in *case* 4. Fig. 6. Glucose tolerance tests in *case* 5. Fig. 7. Glucose tolerance tests in *case* 6.

cent of patients with hyperthyroidism there was no change in the glucose tolerance curve, whether normal or abnormal, while the corresponding figure for the other groups of adults and children was 75.3 per cent and 72.2 per cent, respectively.

The following case records are typical of some of the individual variations in the behavior of the glucose tolerance curve in patients with hyperthyroidism.

Case 1 shows the steady and progressive improvement in carbohydrate metabolism which may occur

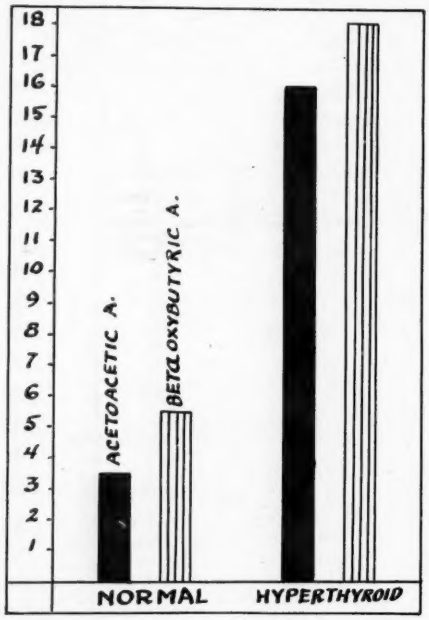

Fig. 8. THE CHANGES IN THE ACETO-ACETIC AND β-OXYBUTYRIC ACID CONTENT OF THE BLOOD IN HYPERTHYROIDISM.

following thyroidectomy even when the hyperthyroidism is severe. The patient was a woman, aged 60, whose B.M.R. was plus 41 per cent, when she was first examined on Dec. 16, 1925. She had lost considerable weight, and had glycosuria and hyperglycemia. The findings in successive glucose tolerance tests during the 12 years following show the steady improvement in the carbohydrate metabolism to a normal level (fig. 2).

Case 2 shows that the response of the carbohydrate metabolism to thyroidectomy may not be immediate. The patient, a man, aged 56, who had previously been obese, had a B.M.R. of plus 50 per cent. He also had hypertension (190 mm. Hg systolic, 78 mm. Hg diastolic), and toxic peri-arthritis. He had glycosuria and slight hyperglycemia. Thyroidectomy was performed on April 26, 1928. On April 25, a glucose tolerance test showed a definite lag in the curve. Eight months later, however, the glucose tolerance curve was normal (fig. 3).

Case 3. In this instance the glucose tolerance curve, repeated 7 months after thyroidectomy, showed an impairment of carbohydrate metabolism which was accounted for by a recurrent goiter. The patient, a man, aged 33, had an adenoma of the thyroid, with hyperthyroidism. His B.M.R. was plus 15 per cent and he had mild hyperglycemia before operation which was performed on Dec. 7, 1927 (fig. 4).

Case 4 shows the effect of hyperthyroidism on carbohydrate metabolism in a case of diabetes. The patient, a man, aged 60, had had diabetes for about 8 years when hyperthyroidism developed during the time he was using iodized salt. The B.M.R. was plus 50 per cent before thyroidectomy was performed, and at the same time, the level of the blood sugar reached its peak (fig. 5).

Case 5 demonstrates the variations in the glucose tolerance curve over a period of more than five years in a case in which diabetes persisted after thyroidectomy. The patient was a woman, aged 50, who had an adenoma of the thyroid with hyperthyroidism. She was obese and displayed glycosuria and hyperglycemia when she was first examined. The basal metabolic rate at that time was plus 36 per cent. The blood pressure was 165 mm. Hg systolic, 90 mm. Hg diastolic. Since the thyroidectomy the patient has remained diabetic, although there has been some fluctuation in the glucose tolerance curve (fig. 6).

Case 6 is interesting because it shows the effect on carbohydrate metabolism of adrenal denervation. The patient was a young woman with hyperthyroidism, aged 23, who at the time of the initial examination, displayed glycosuria, but the blood sugar was normal. The B.M.R. was plus 28 per cent and the blood pressure was 130 mm. Hg systolic, 70 mm. Hg diastolic. Denervation of the right adrenal was carried out on March 31, 1933, and five days later the glucose tolerance curve showed a sharp upswing (fig. 7). Five days after denervation of the left adrenal gland the level of the blood sugar following the ingestion of glucose was much lower.

DISCUSSION

The carbohydrate metabolism tends to be unstable in a considerable number of patients afflicted with hyperthyroidism. In a series of 9000 cases of hyperthyroidism, some disturbance was found in 7 per cent. There are a number of reasons for this finding in hyperthyroidism.

In the first place, patients with hyperthyroidism have an increased rate of metabolism which usually is accompanied by a marked increase in the intake of food consisting largely of carbohydrates. This places an additional load on the insulogenic apparatus, which, if there is a sufficient insulogenic reserve, withstands the added stress. If not, the carbohydrate metabolism is likely to break down under the strain.

The liver in hyperthyroidism is usually poor in glycogen. This has been proven by numerous experi-

mental investigations in which the feeding of desiccated thyroid gland to animals has been shown to result in a reduction of glycogen in the liver (3, 4, 5). Frazier (6) showed that the liver glycogen in control animals was 5.4 gm. per cent; in animals that received thyroid extract, 0.82 gm. per cent; in those that received thyroid plus potassium iodide, 0.12 gm. per cent; and in those that received thyroid plus glucose, 0.17 gm. per cent. Whether this is caused by the increased withdrawal of food reserves from the liver as the result of the higher rate of metabolism, or whether there is a disturbance in the mechanism of storage of glycogen in the liver, is still a question. The presence of mild acidosis may play a part in this phenomenon (fig. 8). The fact that epinephrine, in the presence of a constant hyperglycemia, causes a marked depletion of glycogen from both the liver and the muscles (7) may also have a bearing. Hepatitis was demonstrated by Weller (8) in 50 per cent of a series of necropsies performed on patients with Graves' disease. Thus the presence of hepatitis may be a factor which affects the carbohydrate metabolism in hyperthyroidism.

In hyperthyroidism there is a marked increase in the ketone bodies in the blood (fig. 8). In the presence of acidosis we know that the insulin requirement of diabetic patients under treatment increases, often strikingly. Whether this means that in the presence of a higher concentration of acids less insulin is secreted, or whether there is inactivation of the secreted insulin in circulation, has not been demonstrated clearly[1].

There is also an accumulation of lactic acid in the blood stream in hyperthyroidism. This may be due either to an increased rate of production or to a decreased rate of removal. In normal animals the greater part of lactic acid which escapes oxidation to carbon dioxide and water is carried to the liver for synthesis into glycogen. Buell and Strauss (9) have shown experimentally that in hyperthyroidism the ability of the liver to convert lactic acid to glycogen is impaired. Figure 9 shows the results demonstrated by these authors, that is, the marked decrease of glycogen in the liver and the relative increase of lactic acid in the blood in hyperthyroidism.

From the foregoing facts, it would appear likely that both the pancreas and liver are involved in the disturbance of carbohydrate metabolism which occurs in hyperthyroidism. The exact part played by each of these organs is difficult to estimate. If the liver alone were responsible for the impairment of carbohydrate metabolism observed in hyperthyroidism, we should expect a greater number of patients to return to normal after the hyperthyroidism has been eliminated by operation or treatment. There should be no cases of diabetes resulting from the disturbance ini-

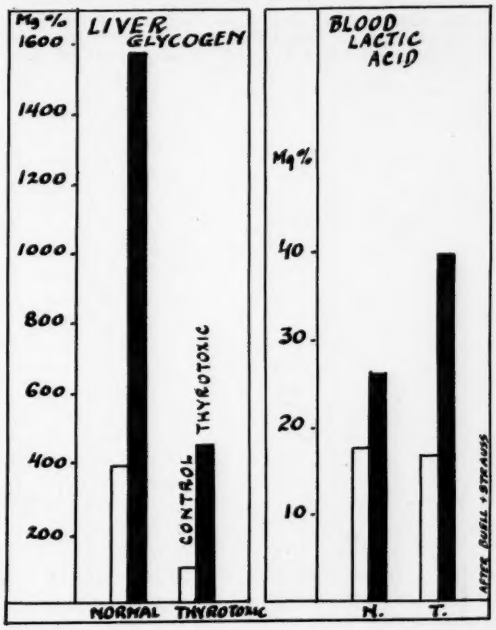

Fig. 9. Changes in the glycogen content of the liver and in the lactic acid of the blood in thyrotoxicosis. (After Buell and Strauss.)

tiated by the hyperthyroidism, and certainly the incidence of diabetes should not be greater in hyperthyroidism than in the general population.

We know, however, that the incidence of diabetes is more than 100 per cent greater in patients with hyperthyroidism. The incidence of diabetes in patients with hyperthyroidism is 2.3 per cent (2), while in the general population it is about 1 per cent. This fact cannot be disregarded. Whether hyperthyroidism, with its increase in metabolism and its accompanying acidosis and hepatitis, also affects the insulogenic function of the islands of Langerhans is a point which needs to be elucidated by further experimental investigations. We know that hyperthyroidism not only causes temporary disturbances in carbohydrate metabolism, but also that it doubles the incidence of diabetes itself. Although we know some of the factors which contribute to this occurrence a

[1] Since the above was written, in recent studies by Lukens and Dohan (Endocrinology, 30: 175. 1942) the authors point out that it is the hyperglycemia which produces hydropic degeneration of the islands. This change is reversible up to this point which means by changing hyperglycemia to normal level. If this stage of hydropic degeneration lasts beyond 3 months, the reversible change is no longer possible and the changes in the islands go on to hyaline degeneration and fibrosis. Thus in as much as we are dealing, in hyperthyroidism, with an acute condition in which the carbohydrate metabolism upset is rarely longer than 3 months, the functional restitution of the beta cells takes place in such a large percentage of cases. It also shows the importance of controlling such an hyperglycemia in order to protect the islands from a possible permanent damage.

complete picture of the mechanism by which it is brought about is still lacking.

REFERENCES

1. JOHN, H. J.: Repeated glucose tolerance tests in children. *J. Pediat.* 14: 737. 1939.
2. JOHN, H. J.: Hyperthyroidism showing carbohydrate metabolism disturbances: ten years study and follow-up of cases. *J. Am. Med. Assoc.* 99: 620. 1932.
3. BÖSL, O.: Über die Einwirkung von Thyroxin auf den Glykogengehalt des Skelettmuskels und der Leber bei Meerschweinchen. *Biochem. Ztschr.* 202: 299. 1928.
4. CRAMER, W., AND R. A. KRAUSE: Carbohydrate metabolism in its relation to the thyroid gland. The effect of thyroid feeding on the glycogen content of the liver and on the nitrogen distribution in the urine. *Proc. Roy. Soc., London, s. B.* 86: 550. 1913.
5. ZIMMERMANN, F.: Beiträge zur Physiologie der Drüse Beiträge zur Aktivierung des Adrenalins durch Thyroxi *Biochem. Ztschr.* 206: 369. 1929.
6. FRAZIER, W. D., AND H. FRIEMAN: Alterations in liver glycoge following thyroid, iodine and glucose feedings. *Surg., Gynec. Obst.* 60: 27. 1935.
7. CORKILL, A. B., H. P. MARKS AND S. SOSKIN: Effects of symp thetic stimulation and of adrenaline on muscle glycogen. *Physiol.* 83: 26. 1934.
8. WELLER, C. V.: Hepatic lesions associated with exophthalm goiter. *Tr. A. Am. Physicians* 45: 71. 1930. Also Editorial *Ann. Int. Med.* 4: 501. 1930.
9. BUELL, M. V., M. B. STRAUSS AND E. C. ANDRUS: Metaboli changes involving phosphorus and carbohydrate in autolyzin gastrocnemius and cardiac muscles of normal, of thyrotoxinized and of adrenalectomized animals. *J. Biol. Chem.* 98: 64 1932.

Studies of the Circulation and Respiration in a Patient with Anasarca Following Administration of Cortin and Sodium Chloride

[Cortical Hormone and Circulation]

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EDEMA IS OF COMMON OCCURRENCE in patients with Addison's disease following treatment with desoxycorticosterone and sodium chloride (1–4). In addition to edema, some patients also exhibit dyspnea, reduced vital capacity, elevated venous pressure and roentgenographic changes suggestive of cardiac dilatation. It has been assumed that heart failure occurs under these circumstances, as a consequence of cardiac dilatation due to overloading the circulation with fluid. However, all of the patients thus far described had the decreased blood volume and abnormally small cardiac size found in Addison's disease. The present report is based on studies made in a patient without Addison's disease who developed massive generalized edema following administration of cortin and sodium chloride.

REPORT OF CASE

B. F. (*B. I. H.* #52040), a 43-year-old man, with a past history of asthma, eczema and eosinophilia for many years and no evidence of adrenal cortical insufficiency, entered the hospital on Jan. 10, 1942, because of dyspnea and generalized edema. Twelve days before entry a dermatologist had prescribed daily doses of 5.0 gm. of sodium chloride by mouth and 1.0 cc. of cortin intramuscularly for the treatment of his eczema. At that time the blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic, the serum protein level was 5.94 gm. per cent and the erythrocyte count was 5,100,000 per cu. mm. The patient received five daily injections of cortin. Five days before entry, marked swelling of the legs was observed. The dose of sodium chloride was reduced to 3.0 gm. daily and cortin was given every other day for two doses. The edema rapidly involved the entire body, dyspnea and orthopnea developed, and the patient therefore entered the hospital. Examination revealed rapid respiration, orthopnea, dyspnea, edema of the face, distended veins in the neck, tachycardia, dullness and greatly diminished breath sounds over the lower portions of the lungs posteriorly, no râles, enlargement of the liver 3.0 cm. below the costal margin with slight tenderness on palpation, abdominal distension, edema of the arms, legs and trunk, and an eczematous lesion of the skin.

Laboratory data. The red blood cell count was 5,400,000 per cu. mm., the hemoglobin was 90 per cent (Sahli), the white blood cell count was 12,100, and the differential was 74 per cent polymorphonuclear cells, 15 per cent lymphocytes, 3 per cent monocytes and 8 per cent eosinophils. The specific gravity of the urine was 1.024. Very large amounts of albumin and small numbers of red and white blood cells and granular casts were observed. The results of the stool examination were negative. Blood non-protein nitrogen level was 37 mg. per cent, serum protein level was 4.42 gm. per cent, and the carbon dioxide combining power was 52 vol. per cent.

Electrocardiographic tracings were normal.

Roentgenograms showed high diaphragm, moderate bilateral pleural effusion and congestive changes in the lungs. The heart was not enlarged.

Clinical course. The patient was given a salt-poor diet with fluids limited to 1200 cc. daily. Edema, hypertension and tachycardia diminished shortly after the patient entered the hospital, disappearing completely by the eleventh day of his stay (fig. 1). On the third day, ammonium chloride, 1.0 gm., was prescribed five times daily, but no detectable change resulted. During the first six days of the hospital stay, the rectal temperature rose to between 100.5° and 101.0° F. every day; thereafter it was normal. Albuminuria rapidly diminished, but did not disappear until several days after all evidences of edema were gone (fig. 1). Granular casts, erythrocytes and leukocytes in the urine likewise were noted after the disappearance of all edema. The blood non-protein nitrogen level was approximately 35 mg. per cent on several occasions. The serum protein level rose to 5.98 gm. on the ninth day of the patient's stay and to 6.54 on the eighteenth day (fig. 1).

METHODS OF STUDY

The cardiac output was measured by the method of Starr and Gamble (5), all measurements being made with the patient in the semi-recumbent position in

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the basal state. The oxygen consumption and respiratory minute volume were measured at the same time. The pulse and respiratory rates were counted 6 to 8 times during each determination. The arm to tongue circulation time was measured by means of decholin (6) and the lung to brain circulation time by means of carbon dioxide (7). The venous pressure was estimated by the direct method of Moritz and von

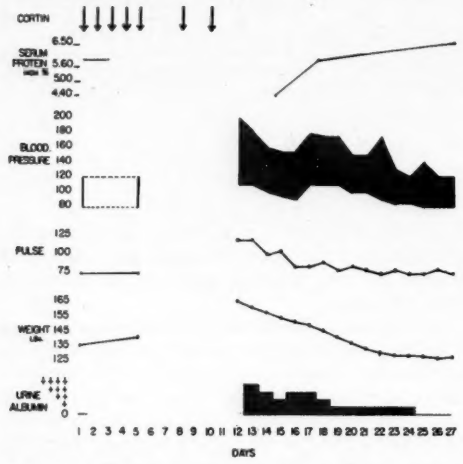

Fig. 1. Response of patient without Addison's disease to therapy with cortin.

Tabora (8). The lung volume and its subdivisions were measured by the method of Christie (9), modified somewhat (10). The arterial oxygen saturation was determined by means of the method of van Slyke and Neill (11), as modified by Fieser (12).

Observations and Discussion

Respiratory dynamics. The respiratory minute volume and rate were increased to twice normal while the patient was markedly edematous; the tidal air, however, was unchanged. The vital capacity was greatly diminished when first studied, the diminution being due to decreases in both reserve and complemental air volumes. The residual and functional residual air volumes were also decreased at this time. All of these volumes returned to normal after all evidences of edema had disappeared. The ratio of functional residual air to total pulmonary capacity was not abnormal at any time; it was 55.4 per cent when first studied, and 53.0 per cent after the patient had recovered. Congestive failure characteristically causes an increase in the ratio of functional residual to total capacity (13) and a decrease in tidal air. Pleural effusion, on the other hand, results in no change in the ratio of functional residual to total capacity (14, 15) and no striking change in tidal air volume. It is clear, therefore, that the changes in respiratory dynamics in the patient of the present report were due to pleural effusion and not to congestive heart failure.

Arterial oxygen saturation. This was not strikingly low when first studied, although a significant increase did occur when the patient recovered. The changes are similar to those seen in other patients with pleural effusions (15).

Venous pressure. The venous pressure was moderately elevated during the height of the patient's illness, returning to normal after his recovery. This change is characteristic both of congestive failure (16) and of pleural effusion (15, 17), so that its occurrence in this instance is not diagnostic.

Cardiac output and circulation time. The cardiac output and arm to tongue and lung to brain circulation times were all within normal limits when the patient was dyspneic, orthopneic and severely edematous. This clearly rules out congestive failure as the cause of these signs and symptoms. There was a small increase in cardiac output following recovery. This resembles the slight increase in cardiac output observed by other authors following resorption of pneumothorax of small or moderate size (18).

Clinical manifestations. The patient's illness was characterized by the rapid onset of marked generalized edema, severe hypertension, dyspnea, orthopnea, profuse albuminuria and the occurrence of erythrocytes, leukocytes and casts in the urine. The serum protein concentration, normal before treatment with cortin and sodium chloride, fell rapidly to the low level of 4.42 gm. per cent. The manifestations, therefore, are similar to those of acute or subacute nephritis or toxemia of pregnancy. It is of interest in this con-

Table 1. Measurements of the respiration and circulation in the presence of anasarca and after recovery

	During	*After*
Decholin circulation time	16.7 seconds	15.6 seconds
CO_2 circulation time	6.8 seconds	
Venous pressure	14.0 cm.	5.1 cm.
Cardiac output	3.76 liters	3.90 liters
Cardiac output/100 cc. O_2 consumed	1.57 liters	1.80 liters
A-V difference	6.36 vol. per cent	5.55 vol. per cent
Stroke volume	44 cc.	51 cc.
Pulse	90	77
Arterial O_2 saturation	93.1 per cent	98.2 per cent
Oxygen consumption	239 cc.	216 cc.
Basal metabolic rate	+5.3 per cent	−1.8 per cent
Respiratory rate	20	10
Respiratory minute volume	10.4 liters	5.06 liters
Tidal air	520 cc.	506 cc.
Residual air	1875 cc.	2420 cc.
Functional residual air	2370 cc.	3850 cc.
Reserve air	495 cc.	1430 cc.
Complemental air	1905 cc.	3410 cc.
Vital capacity	2400 cc.	4840 cc.
Total capacity	4275 cc.	7260 cc.
Functional residual air/total capacity×100	55.4	53.0

nection that other authors (1, 3, 4) have noted the early appearance of edema of the face in patients receiving desoxycorticosterone and sodium chloride therapy for Addison's disease. Edema may occur following desoxycorticosterone medication even if the intake of sodium salts is maintained at normal levels (2). Albuminuria has also been described (1). Ferrebee et al. (1) first suggested that congestive failure, resulting from cardiac dilatation due to overloading circulation with fluid, gave rise to the edema and dyspnea seen in such patients. However, their data (1) show that the extracellular tissue fluid volume increased very much more than the blood volume; indeed in one patient with severe edema and dyspnea, the blood volume was only 300 cc. greater than it had been when the patient was free of these symptoms. Ferrebee et al. (1) stressed increases in cardiac size following treatment with desoxycorticosterone, but McGavack (19) has shown that except for patients in crisis, changes in cardiac size in response to therapy in Addison's disease are not related to variations in blood volume. Conversely, a marked increase in blood volume does not cause cardiac dilatation and congestive failure. Neither patients with polycythemia vera (20), nor patients who have received large intravenous infusions at rapid rates of injection, exhibit cardiac dilatation or clinical or physiological manifestations of congestive failure (21, 22). Similarly, the hypertension which commonly develops after adrenal cortical hormone therapy (2) cannot be considered a consequence of an increase in blood volume (21). It must be concluded, therefore, that the clinical manifestations and physiological findings in patients exhibiting massive edema after therapy with adrenal cortical hormones and sodium chloride are not those of congestive failure secondary to overloading the circulation with fluid. The syndrome resembles closely that produced by the effects of a diffusely active vascular toxin, such as that which causes glomerulonephritis or toxemia of pregnancy. It is worthy of note in this connection that the administration of desoxycorticosterone to a patient with subacute glomerulonephritis aggravated the hypertension and resulted in an increase in the formed elements in the urinary sediment (23).

SUMMARY AND CONCLUSIONS

Studies were made of the clinical manifestations and cardiorespiratory physiology in a patient without Addison's disease who developed anasarca after the administration of cortin and sodium chloride.

The syndrome consisted in severe hypertension, generalized edema, effusions into body cavities, dyspnea, orthopnea, profuse albuminuria and lowering of the serum protein level.

The cardiovascular and pulmonary findings were those of pleural effusion; there was no evidence of congestive failure.

Cortin appears to act as a general vascular toxin in a manner similar to the substances which cause glomerulonephritis and toxemia of pregnancy.

REFERENCES

1. Ferrebee, J. W., C. Ragan, D. W. Atchley and R. F. Loeb: Desoxycorticosterone esters. Certain effects in the treatment of Addison's disease. *J. Am. Med. Assoc.* 113: 1725. 1939.
2. Wilder, R. M.: Progress in treatment of Addison's disease. *Proc. Staff Meet., Mayo Clin.* 15: 273. 1940.
3. Wilson, D. M., E. H. Rynearson and T. J. Dry: Cardiac failure following treatment of Addison's disease with desoxycorticosterone acetate. *Proc. Staff Meet., Mayo Clin.* 16: 168. 1941.
4. Loeb, R. F.: Adrenal cortical insufficiency, *J. Am. Med. Assoc.* 116: 2495. 1941.
5. Starr, I., Jr., and J. C. Gamble: An improved method for the determination of cardiac output in man by means of ethyl iodide. *Am. J. Physiol.* 87: 450. 1928.
6. Winternitz, M., J. Deutsch and Z. Brüll: Eine klinisch-brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion. *Med. Klin.* 27: 986. 1931.
7. Gubner, R., S. Schnur and J. H. Crawford: The use of CO_2 inhalation as a test of circulation time. *J. Clin. Investigation* 18: 395. 1939.
8. Moritz, F., and D. von Tabora: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen. *Deutsches Arch. f. klin. Med.* 98: 475. 1910.
9. Christie, R. V.: The lung volume and its subdivisions. I. Methods of measurements. *J. Clin. Investigation* 11: 1099. 1932.
10. Iglauer, A., and M. D. Altschule: The effect of arterial and venous constriction induced by paredrine (p-hydroxy-a-methylphenylethylamine hydrobromide) on the lung capacity and its subdivisions. *Am. J. M. Sc.* 201: 664. 1941.
11. Van Slyke, D. D., and J. M. Neill: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. *J. Biol. Chem.* 61: 523. 1924.
12. Fieser, L. F.: A new absorbent for oxygen in gas analysis. *J. Am. Chem. Soc.* 46: 2639. 1924.
13. Christie, R. V., and J. C. Meakins: Intrapleural pressure in congestive failure and its clinical significance. *J. Clinical Investigation* 13: 323. 1934.
14. Meakins, J. C., and R. V. Christie: Lung volume and its variations. *Ann. Int. Med.* 3: 423. 1939.
15. Altschule, M. D., and N. Zamcheck: Respiration and circulation in patients with pleural effusion. In press.
16. Altschule, M. D.: The pathological physiology of chronic cardiac decompensation. *Medicine* 17: 75. 1938.
17. Clark, A. H.: A study of the diagnostic and prognostic significance of venous pressure observations in cardiac disease. *Arch. Int. Med.* 16: 587. 1915.
18. Stewart, H. J., and R. L. Bailey: The effect of spontaneous pneumothorax on the circulation in man. *J. Clin. Investigation* 19: 321. 1940.
19. McGavack, T. H.: Changes in heart volume in Addison's disease and their significance. *Am. Heart J.* 21: 1. 1941.
20. Altschule, M. D., M. C. Volk and H. Henstell: Cardiac and respiratory function at rest in patients with uncomplicated polycythemia vera. *Am. J. M. Sc.* 200: 478. 1940.
21. Altschule, M. D., and D. R. Gilligan: The effects on the cardiovascular system of fluids administered intravenously in man. II. The dynamics of the circulation. *J. Clin. Investigation* 17: 401. 1938.
22. Altschule, M. D., D. R. Gilligan and N. Zamcheck: The effects on the cardiovascular system of fluids administered intravenously in man. IV. The lung volume and pulmonary dynamics. In press.
23. Derow, H. A.: Personal communication.

COMMUNICATIONS TO THE EDITORS

Precautions for Pituitary and Thyroid Medication: Three Case Reports

Hypertension developing during thyroid and pituitary medication. A psychoneurotic maiden lady of 42 was examined January 2, 1936. She had sought treatment the preceding February for obesity, chronic fatigue and rheumatism. At that time her temperature was 99° F., pulse 82, blood pressure 145/95 mm. Hg, weight 211 pounds. The obesity was of the girdle type. Treatment had consisted of salicylates, foreign protein, sulphur and the usual remedies for rheumatism and arthritis. At the same time she had been put on a regime of reduced caloric intake and liberal doses of thyroid. Once or twice a week pituitary extracts had been injected, 0.5 cc. of an unstandardized extract of the anterior lobe and 0.5 cc. of the obstetrical variety of posterior lobe extract. During the eleven months she had lost 58 pounds in weight, but the symptoms were unchanged and the blood pressure had risen to 180/110 mm. Hg. Cessation of the thyroid and pituitary therapy had no effect on the blood pressure, and none of the measures usually employed for the control of essential hypertension has been effective. As a matter of fact, her blood pressure has risen and has since been as high as 210/110 mm. Hg.

She had had attacks of rheumatic fever at 15, 27 and 32 years of age and did not menstruate for 3 years following an appendectomy when she was 32 years old.

The patient had a marked urticarial outbreak a few hours after the first dose of posterior lobe extract, but when another manufacturer's product was used she tolerated it without unpleasant symptoms. The injections throughout the eleven months of treatment had not caused any discomfort. The hypertension was not accompanied by any of the symptoms often associated with or attributed to it.

Urticarial reactions to posterior lobe extracts are unusual and comparatively few cases are reported in the literature. In twenty years of active endocrine practice I have seen only four cases. Unfortunately we did not learn in any of these cases from what animal species the pituitary extracts had been prepared.

It cannot be said that the thyroid and pituitary injections caused the hypertension. As a matter of fact, we have had a few obese patients with hypertension whose blood pressure was reduced to normal levels by precisely the same treatment as this woman had. In some cases the blood pressure falls markedly after injections of extracts of either the anterior or posterior pituitary lobe. This case is cited only to call attention to the advisability of watching the blood pressure when a patient is on a prolonged regime of thyroid and pituitary medication.

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Hyperglycemia after injections of pituitary extracts. On April 25, 1941, a woman of 49 was seen who complained of obesity, limited largely to the lower half of the body, slight menopausal symptoms and constipation. She had gained 37 pounds since her marriage at the age of 34, when she weighed 96 pounds. She was 60¾ inches in height. Her B.M.R. was minus 7 per cent. The fasting blood sugar was 120 mg. per cent. After ingestion of 100 gm. of glucose, the blood sugar was 238, 187 and 164 mg. per cent at ½, 1½ and 2½ hours. No glycosuria occurred. The following day she was given 0.5 cc. of an unstandardized extract of the anterior lobe and the blood sugar rose in an hour from a fasting level of 125 to 230.7 mg. per cent. The day following she was given 0.3 cc. of obstetrical pituitrin and the blood sugar rose in one hour from a fasting level of 120 to 187.5 mg. per cent. No glucose was given with these tests. The rise in blood sugar presumably was due to the effects of the pituitary extracts. This type of response to pituitary extracts is not unusual and occurs often enough to warrant testing the patient's response to these substances before they are used as therapeutic measures. Pituitary extracts should not be administered to patients showing high blood sugar values during the glucose tolerance test nor to those exhibiting a marked rise in blood sugar after the injection of such extracts. While patients are taking thyroid and pituitary extracts, the blood pressure should be checked frequently and blood sugar determinations occasionally made.

In May the patient was given 10,000 I.U. of estrogen* in 2000 unit doses at approximately four-day intervals. In June she received 2000 units on the 2nd, 5th, 9th and 12th. There was no treatment in July, August and September except with estrogenic hormone orally, 5000 units every third day. She had 2000 I.U. of estrogen on October 4th, 10th, 16th and 27th and on November 10th, 14th, 17th and 27th. On December 1st another glucose tolerance test was made. The fasting blood sugar was 112 mg. per cent. After 100 gm. of glucose the blood sugar was 164.2, 135.8 and 94.5 mg. per cent at ½, 1½ and 2½ hours, respectively, after the ingestion of the glucose. There was no glycosuria.

The administration of even small doses of posterior lobe extract within four days of the onset of a menstrual period will usually cause marked abdominal pain with the flow.

Thyroid given to obese young women frequently may upset the menstrual function and cause the periods to be delayed or even suppressed for a few months.

* The estrogen (Amniotin) was supplied by E. R. Squibb and Son, New Brunswick, N. J.

Diabetes mellitus developing during treatment for hypogonadism. A boy, aged 14, was seen August 7, 1940, complaining that only one testicle was in the scrotum. The mother said he was sensitive, cried easily and lacked aggressiveness. In his early years he had had whooping cough, measles, scarlet fever and chicken pox. He was of normal height and about 10 pounds overweight. The genitalia were underdeveloped, but both testicles were in the scrotum. The B.M.R. was minus 14 per cent. The blood count and urinalysis findings were normal.

He was given thyroid, one grain per day, APL gonadotropin, 100 units twice a week and anterior pituitary extract 0.5 cc. once a week. He received 8 injections in August and 3 in September. He was then given an extract of anterior pituitary in 0.5 cc. doses 4 times in September, 8 times in October, 9 times in November and 8 times in December, 1940; 7 times in January, and 8 times in February, 1941.

In March he was given 6 injections of 100 U of APL gonadotropin. In April, because of a gain in weight, three minims of pituitrin was added to the APL. He received 8 injections in April, 6 in May and 4 in June.

Because the genital development was slow the APL gonadotropin was increased to 200 U and 5 minims of an extract of posterior pituitary was given with it four times in June. He received three injections in July.

During a long automobile trip in the latter half of July he noticed marked thirst and between July 1 and August 5, 1941, he lost five pounds in weight. The urine had been examined frequently and the findings were normal May 27, 1941. On August 5 there was marked glycosuria, some acetone and diacetic acid. The blood sugar was 333 mg. per cent. On a diet of carbohydrate 140, protein, 90 and fat, 110 gm. 30 U of insulin are required to keep the blood sugar within normal limits and the urine sugar-free. The patient has made a normal growth in height and the genitalia are now of normal size.

While the literature warns that glycosuria may develop in the course of such treatments, this is the first case I have seen. Dr. Chester Guy saw one such case. The glycosuria appeared shortly after treatment with pituitary hormones was started and disappeared under dietary restrictions. Such cases offer further support for the belief that the pituitary gland plays some part in the syndrome of diabetes mellitus.

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Abstracts of
CURRENT CLINICAL LITERATURE

Editor: DANIEL A. McGINTY. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, EMMERICH VON HAAM.

GONADS

WIESBADER, H.

Oral therapy with pregneninolone in functional uterine bleeding. *Am. J. Obst. & Gynec.* 42: 1013, 1941.

Twenty patients were treated, the steroid being employed to stop bleeding; the highest daily dosage was 50 mg. It was found that 280 to 350 mg. were required to stop bleeding. Two patients yielded progestational responses. It is reported that 200 to 240 mg. of pregneninolone given during the latter half of the cycle will maintain cyclic and normal bleeding.—*E.C.H.*

WEISMAN, A. I., AND A. SCHWARZ.

Intersexuality proved by operation and microscopic examination. *J. Am. Med. Assoc.* 117: 2248. 1941.

A patient exhibiting unusual intersexuality had all the aspects of a female, but her gonads were definitely abdominally retained immature testes, and there was complete absence of ovarian tissue. Sufficient numbers of complete reports of such cases, when carefully studied may be capable of eventually explaining the etiology of such unnatural switches in nature.—*C.P.*

HYPOPHYSIS

BOEHM, E. E.

Use of zipper in Friedman test. *Am. J. Clin. Path. Tech. Sec.* 5: 168. 1941.

The author recommended use of an ordinary 4 inch zipper placed in a midline incision in a rabbit for repeated examinations during the Friedman test. The first changes recognizable in the ovaries are small reddish-black spots which become noticeable as early as 10 hours after injection. The reaction reaches its height after 45 to 75 hours and the ovaries return to normal after 10 to 13 days. When the zipper is opened the first time numerous adhesions may be noted. After removing the zipper the incision heals rapidly.—*E.v.H.*

BREWER, J. I., H. O. JONES AND J. H. SKILES, JR.

Effect of gonadotropic substance on ovulation. *J. Am. Med. Assoc.* 118: 278. 1942.

A group of 24 female patients awaiting abdominal operation was treated with gonadotropic substance from PMS, and a group of 22 female patients was observed as controls. Only 2 of the treated patients showed signs of ovulation at operation. No multiple or new ovulations were induced. Ovulation occurred more uniformly in the control group.—*C.P.*

FRASER, R., AND PATRICIA H. SMITH.

Simmonds' disease or panhypopituitarism (anterior); its clinical diagnosis by the combined use of two objective tests. *Quart. J. Med.* (New Series) 10: 297. 1941.

The authors advocate the use of 2 tests as criteria in distinguishing Simmonds' disease from other similar pathologic states. The first was based on the patients' sensitivity of response to insulin, this being given intravenously, 0.1 unit per kilogram of body weight, after a 12-hour fast, a standard carbohydrate diet having been administered for the previous 4 days. Results were judged primarily by the speed of the fall in blood sugar and of recovery to the fasting level. In Simmonds' disease, the return to fasting blood sugar level is delayed and the 24-hour urinary excretion of 17-ketosteroids is below 0.5 mg. There are other disease conditions in which the response to insulin may be similar to that of Simmonds' disease or the 17-ketosteroid output may be extremely low. The authors present the results of these 2 tests in 10 cases which they diagnosed as having panhypopituitarism and in 15 other cases with allied syndromes including primary myxedema and anorexia nervosa.—*J.E.H.*

TWOMBLY, G. H., H. M. TEMPLE AND A. L. DEAN.

Clinical value of the Aschheim-Zondek test in the diagnosis of testicular tumors. *J. Am. Med. Assoc.* 118: 106. 1942.

A study of 203 cases of testicular tumor in which quantitative A-Z tests were done by the method of Ferguson and a study of 42 cases in greater detail, with a larger number of mice per assay level, revealed little correlation between the amount of gonadotropic hormone found in the urine and the histologic type of the tumor. Presence of chorionic gonadotropic hormone in the urine means an active tumor somewhere in the patient and suggests a bad prognosis.—*C.P.*

PANCREAS

BEARDWOOD, J. T. JR., AND G. P. ROUSE, JR.

Diabetic acidosis. *J. Am. Med. Assoc.* 117: 1701. 1941.

The mortality rate for 200 cases of diabetic acidosis among 1,865 diabetic patients was 23.6% when cases with complications were included; when such cases were eliminated, it was 5%. Treatment used was M/6 Na lactate with adequate volumes of NaCl solution.—*C.P.*

GREENE, J. A., AND L. W. SWANSON.

The utilization and effect of added dextrose. *J. Am. Med. Assoc.* 118: 364. 1942.

Carbohydrate was added to the usual regimen of patients with controlled diabetes in an unsuccessful attempt to differentiate between possible types of diabetes. Only 1 of the 56 patients failed to utilize the added sugar, whereas 18 required less insulin. Since such improvement indicated a beneficial effect, extra carbohydrate was added to the diets of 36 patients with uncontrolled diabetes. Only 1 failed to utilize the added sugar, whereas the urine of 15 promptly became free of sugar. There was no uniform response of blood-sugar levels. It is postulated that depletion of the sugar stores of the body further reduces the ability of many diabetic patients to utilize dextrose and that the correction of this depletion improves the diabetes in such cases.—*C.P.*

THYMUS

BLALOCK, A., A. M. HARVEY, F. R. FORD AND J. L. LILIENTHAL, JR.

The treatment of myasthenia gravis by removal of the thymus gland. *J. Am. Med. Assoc.* 117: 1529. 1941.

Confirmation of earlier operations where myasthenic patients were improved by thymectomy is provided by 6 additional cases. In 3 the improvement has been gradual, but definite. The authors conclude that thymectomy may be merely the breaking of a chain of abnormal events, although the data may indicate that the thymus is a gland with a functional internal secretion.—*C.P.*

THYROID

BREITBARTH, B.

Study on the phosphate metabolism in congenital athyroidism. *Ztschr. f. Kinderh.* 62: 52. 1940.

Lack of thyroid in the organism is followed by a decrease in inorganic P and an unfavorable Ca:P balance. On administration of thyroid in juvenile myxedema the low P content becomes normal or increased and on discontinuation of treatment this effect lasts for some time. Thyroid causes a retention of P and Ca, but does not influence N metabolism. In balance studies on 10 thyroidectomized dogs the deficiency in thyroid was carefully compensated and evenly adjusted. On administration of thyroid the Ca and P balance is restored after a latent period and the excretion of both Ca and P in the urine is decreased. With subsidence of thyroid application, more Ca and P is excreted with the feces.—*Erich Kaufmann (courtesy Chem. Abstracts).*

BROWN, R. B., E. P. PENDERGASS AND E. D. BURDICK.

The gastrointestinal tract in hyperthyroidism. *Surg., Gynec. & Obst.* 73: 766. 1941.

In human hyperthyroidism there is relative to the normal an increased incidence of achlorhydria, increased prominence of gastric rugae, a questionable increase in the time of onset of gastric emptying but a delay in the time required for complete evacuation of gastric contents and an increase in both tone and motility of large and small intestine.—*A.T.K.*

ENGEL, M. B., I. P. BRONSTEIN, A. G. BRODIE AND P. WESOKE.

A roentgenographic cephalometric appraisal of untreated and treated hypothyroidism. *Am. J. Dis. Child.* 61: 1193. 1941.

In a study of 13 selected cases of hypothyroidism roentgenograms were made according to the technic of Broadbent. Bone development was judged by the Todd Standards. Craniofacial, dental and carpal ossification patterns of development of untreated children with hypothyroidism lag behind those of children given thyroid therapy. The deficiency lies in the occipital, parietal and, to much less extent, frontal area. The cranial base is shortened, and the spheno-occipital synchondrosis and the sutures of the vault are abnormally wide. The face shows a generalized retardation of growth as a result of the slowed velocity of growth of its components, that is, the mandible, the maxilla and the nasal bone. Teeth are delayed in eruption, without malformation. Differentiation and ossification of carpal centers are disturbed and retarded, and roentgenograms show persistence of infantile characters. Craniofacial dental and carpal patterns of development in untreated children with hypothyroidism are rtearded. The differences from normal are merely an accentuation of those noted between treated and untreated cretins. Children with hypothyroidism treated regularly since early childhood closely approach normal levels of craniofacial and dental development. Thyroid deficiency affects craniofacial growth by retarding velocity rather than by modifying pattern.—*M.B.G.*

EZICKSON, W. J., AND L. M. MORRISON.

Role of liver and thyroid as metabolic factors in production of renal calculi. *J. Urol.* 46: 359. 1941.

Fifty-nine patients with renal or ureteral calculi were studied. Of these 61% showed an abnormal B.M.R. 50% hypercholesteremia and 59% liver dysfunction.—*J.C.D.*

FOGGIE, W. E.

A lingual thyroid: myxoedema following its removal. *Edinburgh M. J.* 48: 662. 1941.

A woman, 36 years old, had a cyst, which was causing mechanical interference, removed from the base of her tongue. The cyst wall was made up of thyroid tissue and no cervical thyroid could be detected. Myxedema developed and the patient was in coma when seen seven months after the operation. The symptoms were permanently relieved by thyroid feeding. The occurrence and significance of this rare condition are discussed.—*J.C.D.*

HILDEBRAND, ALICE G., AND E. J. KEPLER.

Familial periodic paralysis associated with exophthalmic goiter. *J. Nerv. & Ment. Dis.* 94: 713. 1941.

Familial periodic paralysis is a rare condition, 240 cases in all having been reported. It is marked by irregularly

occurring attacks of somatic muscular paralysis and inexcitability without sensory or psychic disturbances and good health in intervals between attacks. In the case reported, with the onset of exophthalmic goiter, the patient, who had previously suffered from occasional attacks of paralysis, began having frequent and severe attacks. The severity of the attacks was found to be closely correlated with the degree of depression of serum K. Attacks could be induced by injections of glucose-saline or by other agents which reduce blood K. Lugol's solution having been found inefficacious in relieving the disorder partial thyroidectomy was performed with entire relief. The hyperthyroidism was regarded as unmasking rather than causing the paralytic disorder.—*R.G.H.*

HIRSCHBERG, N., AND I. P. BRONSTEIN.

Note on a cretin's response to typhoid inoculation. *Am. J. M. Sc.* 202: 333. 1941.

In an investigation of the relationship of the thyroid to immunity a 22-year-old cretin was given typhoid vaccine. Subsequently repeated agglutination tests gave negative results. Following thyroid treatment at ½ to 2 grains daily strong agglutination reactions were obtained. No influence upon phagocytic activity could be detected.—*R.G.H.*

LERMAN, J.

The physiology of the thyroid gland. *J.A.M.A.* 117: 349. 1941.

In this review article the phvsiology is dissussed under the following headings: histophysiology, thyroid hormone, potency of various fractions, blood I, relation to other endocrine glands, and the relation of thyroid to nutrition.—*C.P.*

MASTER, A. M., AND JENNY STRICKER.

Myxedema heart. Report of a case. *Ann. Int. Med.* 15: 123. 1941.

A case of hyperthyroidism is described in which the classical signs of myxedema heart appeared 10 years after operation for hyperthyroidism. After 6 weeks of thyroid medication the patient's general condition improved markedly, the B.M.R. became normal, dyspnea, fatigability and cardiac abnormalities disappeared. The heart, previously enlarged and of typical water-bottle appearance, became normal in size and configuration. Simultaneously the E.K.G. which had shown the characteristic low voltage of all deflections (QRS 4 mm.) became normal. Pericardial effusion is presented as a possible cause for the enlarged heart, the diminished cardiac pulsations and the low voltage E.K.G. in myxedema heart.—*Author's abstract.*

RIGGS, D. S., E. F. GILDEA, E. B. MAN AND J. P. PETERS.

Blood iodine in patients with thyroid disease. *J. Clin. Investigation* 20: 345. 1941.

The blood I in 31 patients with hyperthyroidism ranged between 6.4 and 21.9 per cent; there was no overlapping with the normal range of 2.4 to 4.2 per cent. Seven patients with nodular goiters with no symptoms of overactivity showed normal blood I. Elevated blood I values were invariably found in hyperthyroid patients, but high values were sometimes found in the absence of hyperactivity.—J. B. BROWN. (*courtesy Chem. Abstracts*).

SALTER, W. T., A. M. BASSETT AND T. S. SAPPINGTON.

Protein-bound iodine in blood. Its relation to thyroid function in 100 clinical cases. *Am. J. M. Sc.* 202: 527. 1941.

A series of 100 cases of suspected thyroid disturbance and 10 control individuals has been analyzed from the standpoint of final clinical diagnosis, B.M.R. and plasma protein-bound I. When the first two of these criteria are in agreement, there is a close correlation between the plasma I and the B.M.R. Such cases amount to 71% of the entire group studied. Of the remaining 29%, the B.M.R. often did not clearly reflect the clinical status and the plasma protein-bound I proved much more reliable. This was particularly true in the group of "Graves' disease without hyperthyroidism" in which the B.M.R. ranged from −20 to −40%, but the plasma protein-bound I was normal. These data therefore constitute additional evidence for the possible dissociation of physiologic hyperthyroidism and clinical Graves' disease. In hypothyroidism, plasma protein-bound I appears to be a highly reliable criterion for confirming lack of thyroid hormone, even when full-blown myxedema is absent. It has been emphasized that the simplified chemical procedures employed are partly empirical. Their use has been justified by their consistency with clinical data, but due care should be exercised in comparing the data with the results obtained by other methods.—*Authors' summary* (*R.G.H.*)

SCHMIDT, C. R., W. S. WALCH AND V. E. CHESKY.

Liver insufficiency in toxic goiter and its treatment. *Surg., Gynec. & Obst.* 73: 502. 1941.

Liver function was tested by the hippuric acid test (oral) of Quick in 207 consecutive patients with goiter. Some impairment of liver function appeared in 55 per cent, 17 per cent showed reduction below 70 per cent of normal. The correlation between elevation of B.M.R. and depression of liver function was not perfect. Those with long standing hyperthyroidism with normal or slightly elevated B.M.R. were likely to have impaired liver function. While the role of heart failure in contributing to hepatic damage is recognized, this group is not specifically analyzed for this factor. Thyroid crisis and toxic psychosis were preceded or accompanied by severe liver insufficiency. Thyroidectomy was followed by a transient depression of liver function not due to sedative or local anesthetic. Liver function may be improved by a rather miscellaneous aggregate of procedures significantly called the 'works,' comprising added glucose with insulin, bile salts, liver concentrates and vitamin B.—*A.T.K.*

SCHWITTAY, A. M.

Occult hypothyroidism in Wisconsin women. *Wisconsin M. J.* 40: 475. 1941.

All patients with menstrual disorders should have

B.M.R. determinations made, as a safeguard against missing those whom thyroid therapy would benefit. Use of the therapeutic test of thyroid medication rendered clinical results as good, in many cases, when the B.M.R. was −8% to −10% as when it proved considerably lower. The menstrual disorders of patients with depressed B.M.R. were alleviated by thyroid therapy.—*H.O.H.*

Sherrill, J. W., and E. M. McKay.

Hypothyroidism and bladder function. *J. Urol.* 46: 34. 1941.

Twenty-four rats, 170 days old, were divided into 3 equal groups. One group was thyroidectomized, one fed desiccated thyroid and the third kept as controls. The results are tabulated and illustrated with silhouettes of the bladder. The authors summarize: "Atony of the bladder observed in patients suffering from hypothyroidism stimulated an experimental study of the relation of these conditions in the albino rat. Hypothyroid rats regularly showed bladder atony as measured by the filled area shown by a radio-opaque compound in urine; bladder emptying time and the lowered ability to sustain an artificial increase in the intra-bladder pressure."—*J.C.D.*

Smokvina, M.

Results of irradiation of the pituitary in Graves' disease and other forms of hyperthyroidism. *Radiologia Clinica* 9: 151. 1940.

The author describes the results of the recent experimental clinical and radiological investigations as to the action of the pituitary body in the production of Graves' disease and other conditions of hyperthyroidism. He reports the result of irradiation by X-rays carried out between 1932 and 1939 on 50 such cases, at first only in women during the climacteric, but later also in younger women and in men. He describes fully the technic used at the Zagreb Institute. He considers that in such cases, when irradiation of the thyroid and thymus glands has not succeeded, the pituitary body should be treated, even when the condition of the patient has become worse, and certainly before an operation is performed.—*Clinical abstracts.*

Soffer, L. J., C. Cohn, E. B. Grossman, Mildred D. Jacobs and H. Sobotka.

Magnesium partition studies in Graves' disease and in clinical and experimental hypothyroidism. *J. Clin. Investigation* 20: 429. 1941.

In a series of 50 patients with Graves' disease a large proportion show a definite increase in nondiffusible Mg, the bound fraction varying between 25 and 61.6 per cent of the total serum Mg. There was no correlation between bound Mg and the B.M.R. In patients with Graves' disease of more than 2 years duration the nondiffusible Mg frequently tends to approximate normal levels. After treatment with I there is a marked drop in bound Mg, which is further lowered after subtotal thyroidectomy. In patients with myxedema, as well as with thyroidectomized dogs, nondiffusible Mg is low or even absent. This returns to normal after administration of thyroid extract or thyroxine. The increase or decrease of bound Mg occurs at the expense of the ionizable fraction, since the total serum Mg remains unaltered.—*J. B. Brown (courtesy Chem. Abstracts).*

Starr, P., and H. Pomerenze.

Therapeutic studies in hyperthyroidism. *Ann. Int. Med.* 15: 226. 1941.

The effect of various medicaments administered, with chronological metabolism charts, is reported. An example of abrupt spontaneous remission after interruption of lactation is described. Desiccated thyroid, thyreotropic hormone, vitamin C, vitamin A, and testosterone were used in individual cases in very high doses, without benefit. Chorionic gonadotropin was given 2 patients in whom remissions of hyperthyroidism occurred.—*Paul Starr.*

Steiner, M., and A. L. Newbomb.

Enlargement of the thyroid gland in juvenile patients with diabetes mellitus. *Am. J. Dis. Child.* 61: 458. 1941.

The occurrence of a palpable thyroid gland in juvenile diabetic subjects and its relation to the occurrence of diabetes and thyroid disease in the family have been investigated. Twenty per cent of the 128 subjects had a definitely palpable thyroid gland, and of these 50% had a history of diabetes and 80% a history of thyroid disease in the family, as compared with 19 and 12% respectively of those subjects with normal thyroids.—*M.B.G.*

Sutton, R. L.

Acne vulgaris a pustular lipoidosis. Successful treatment based on control of lipoid metabolism by low fat diet and thyroid extract. *South. M. J.* 34: 1071. 1941.

The use of thyroid extract to tolerance in all cases is described in connection with the dietary measures used. —*J.C.D.*

Talbot, N. B., G. Hoeffel, H. Shwachman and E. L. Tuohy.

Serum phosphatase as an aid in the diagnosis of cretinism and juvenile hypothyroidism. *Am. J. Dis. Child.* 62: 273. 1941.

Normal value for serum phosphatase for children 2 to 10 years of age is approximately 7 U. with a range of from 5 to 14 U. per 100 cc. of serum. The level of phosphatase in the plasma or serum is definitely higher in children than in normal adults. The highest level is probably in the 4th or 5th month of life. The level tends to be depressed below normal limits in infants and children with untreated hypothyroidism (1.3 to 4.3 Bodansky U. in cretinism and 2.7 to 5.3 in juvenile hypothyroidism in this series). It is normal in mongolism. Since administration of adequate thyroid therapy raises the value, it is suggested that the level of serum phosphatase is a reliable index of thyroid deficiency in infancy and childhood.—*M.B.G.*

THOMPSON, W. O.

Thyroid dysfunctions and their treatment. *J.A.M.A* 117: 441. 1941.

Thyroid dysfunction and pathology are discussed in this review article under the following headings: *a*) Primary and secondary hypofunction, *b*) Hyperfunction, *c*) Pathological states without altered function. The treatment, differential diagnosis, and complications of thyroid disorders are also discussed. There are also paragraphs on developmental anomalies, inflammatory conditions, and neoplasms of the thyroid.—*C.P.*

TOBIAS, M., AND L. STOCKFORD.

Measure of metabolic speed in children. *Am. J. Dis. Child.* 61: 675. 1941.

The assessment of delay in carpal development is not a measure of "slow metabolic speed." Determination of the level of total cholesterol is a simple and valid measure of a low level of maintenance B.M.R. activity in children. When the B.M.R. is within the so-called normal limits of +10 and −10%, its normality must be verified by measures of both the total cholesterol and the skeletal development. Determinations of B.M.R. are less reliable than are determinations of total cholesterol as measures of "slow metabolic speed."—*M.B.G.*

WASS, S. H.

Di-iodotyrosine in treatment of Graves's disease. *Lancet* 34. 1941.

In previously untreated cases the use of di-iodotyrosine as a preoperative measure was restricted to the most severe cases. In these it appeared to be entirely satisfactory, but showed no decided superiority over inorganic I. In patients who had had long courses of I before being referred to the surgeon, di-iodotyrosine produced remissions of sufficient degrees to allow of safe surgery. In this type of case the drug seems to produce better effects than can regularly be expected from iodine alone. In 2 cases a further remission was produced with a second course of di-iodotyrosine, but these figures are too small to allow of any definite conclusion. Thus, it seems to be possible to control the symptoms of hyperthyroidism by giving di-iodotyrosine periodically to patients awaiting operation, and still to get the patient into a good state for surgery when the time arrives. In hospital practice the drug may be very useful in this way, and further work may prove it of value in the routine medical treatment of Graves's disease.—*Courtesy Clin. Abstracts.*

WOKES, F.

The subcutaneous implantation of thyroxine tablets. *J. Pharmacol. & Exper. Therap.* 14: 165. 1941.

The effect of implanted thyroxine lasted about 3 weeks, and, since effects of this duration can readily be obtained by oral doses of thyroid, there is no obvious advantage in implanting tablets.—*H. A. McGuigan (courtesy Biol. Abstracts).*

YARDUMIAN, K. Y., AND N. M. WALL.

The relationship between blood cholesterol, sugar tolerance, and basal metabolic rate in thyroid disease. *Pennsylvania M. J.* 45: 239. 1941.

In cases of thyroid disease, with a rise in the B.M.R. there is a definite trend toward a lower serum cholesterol and decreased tolerance to glucose. And the reverse is true with a fall in the B.M.R. These trends are general, but in the more extreme cases the tendency towards a closer relationship becomes more pronounced. Exceptions are not uncommon.—*I. B.*

ZONDEK, H., M. MICHAEL AND A. KAATZ.

The capillaries in myxedema. *Am. J. M. Sc.* 202: 435. 1941.

In 8 women suffering from myxedema with typical mixedema hearts, the peripheral circulatory portion was subjected to exact investigation. In 7 cases the capillaries (ungual limbus) were markedly changed, the most striking feature being pronounced narrowness of the limbs. In some instances the loops only were recognizable. The number of visible capillaries was reduced. On thyroidin administration, the capillary picture as well as the clinical symptoms and the circulation time gradually returned to normal. No parallelism, however, could be established between the behavior of the capillaries on the one hand, and the general condition and the acceleration of the circulation time on the other hand. In the light of this evidence, the conclusion may be drawn that thyroidin is active in opening the arteriovenous anastomoses. Apparently the cross-section of the anastomoses as well as that of the capillaries is reduced in cases of myxedema, which is comprehensible in view of the abnormally reduced O_2 requirements. In many cases myxedematous patients suffering from precordial pains similar to anginal states are likewise relieved by thyroidin administration. In this case, thyroidin is assumed to bring about a dehydration of the heart muscle (Zondek) and thus an increase in the blood supply of the heart. It is, therefore, suggested that development of precordial pains in myxedematous patients is not, as a rule, due to sclerotic changes of cardiac vessels, as generally assumed, but to mechanical impairment of coronary flow.—*Authors' summary.*